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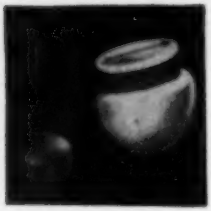

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We made the lady such a glass and it has been her pride and joy since.

Some time later a man, who does a great deal of motoring but has an ingrown fear of driving with bifocals, was given a hand monocle to allow him to see a road map without fumbling around for another pair of glasses. He ordered a second lens to keep in his vest pocket for use when he did not have sustained reading to do but might want to see a price ticket or glance through a letter. He was quite satisfied with both lenses.

In the scientific corner some years ago, we mentioned how a single lens mounted in the frame part of a Bell occluder had done a job for a professional photographer. This chap specialized in interiors, and many times in order to take in an entire room was backed into a corner with his eyes only a few inches from the ground glass of his camera. A plus five sphere allowed him to focus his camera accurately at approximately four and one-half inches from the glass.

If we consider a hand monocle as doing about the same job for both men and women as the lorgnette does for women, we have a new, correct concept of its usefulness. Every one we know who has a hand monocle or clip on monocle uses it often, nicely and apparently "wouldn't be without it."

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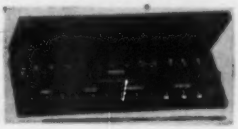

These test objects are adapted for either tangent screen or for perimetry and campimetry. The test objects are white and colored spheres mounted on non-reflecting pins. The latter are held in split wands to keep the examiner's hand out of the visual field. The test objects come in a range of sizes from ½mm. to 20mm. both white and colored.

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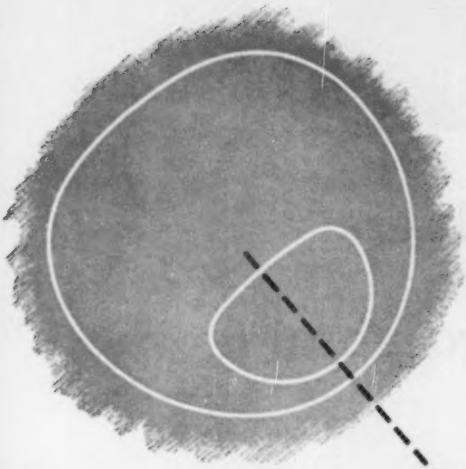

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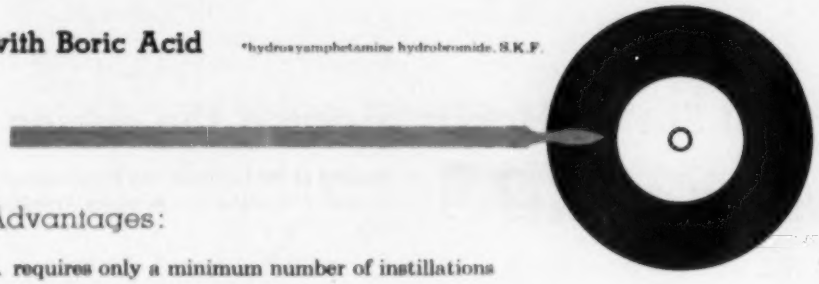

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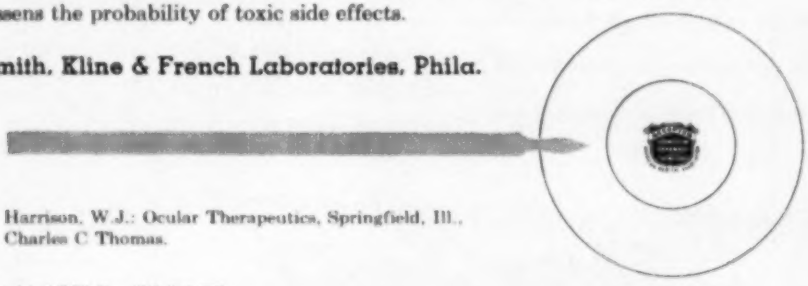

1. Harrison, W.J.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas.

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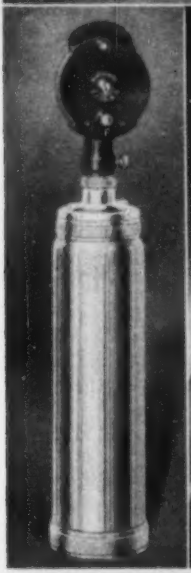

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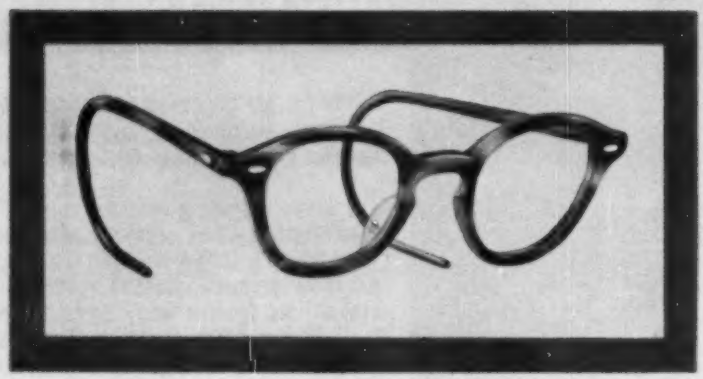

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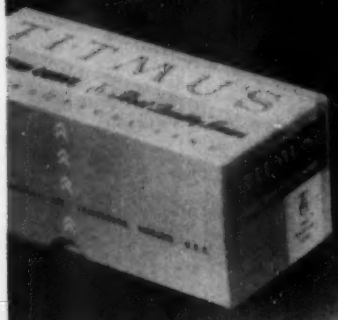

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VERNAL CONJUNCTIVITIS

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M. N. BEIGELMAN, M. D.

Clinical Professor of Surgery (Ophthalmology), University of Southern California School of Medicine

Senior Attending Ophthalmologist, Cedars of Lebanon Hospital

Attending Eye Pathologist, Los Angeles County Hospital

With a Foreword By

SIR W. STEWART DUKE-ELDER

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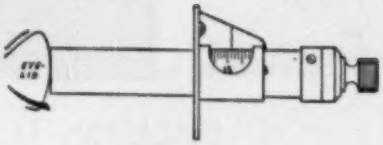

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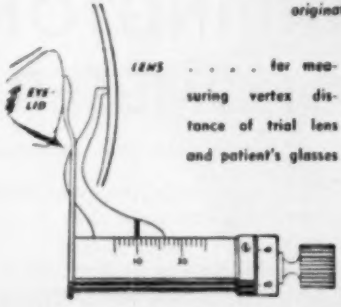

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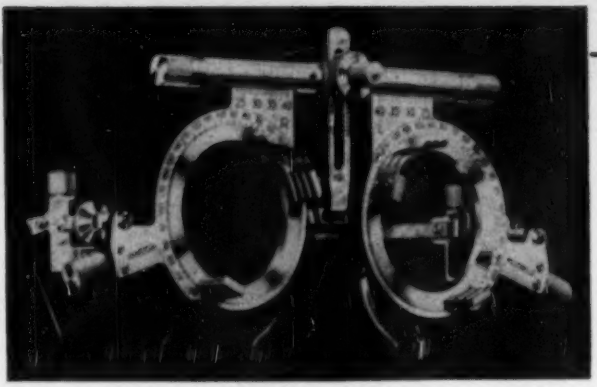

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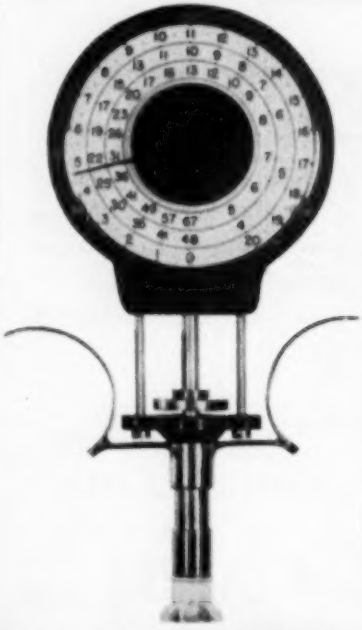

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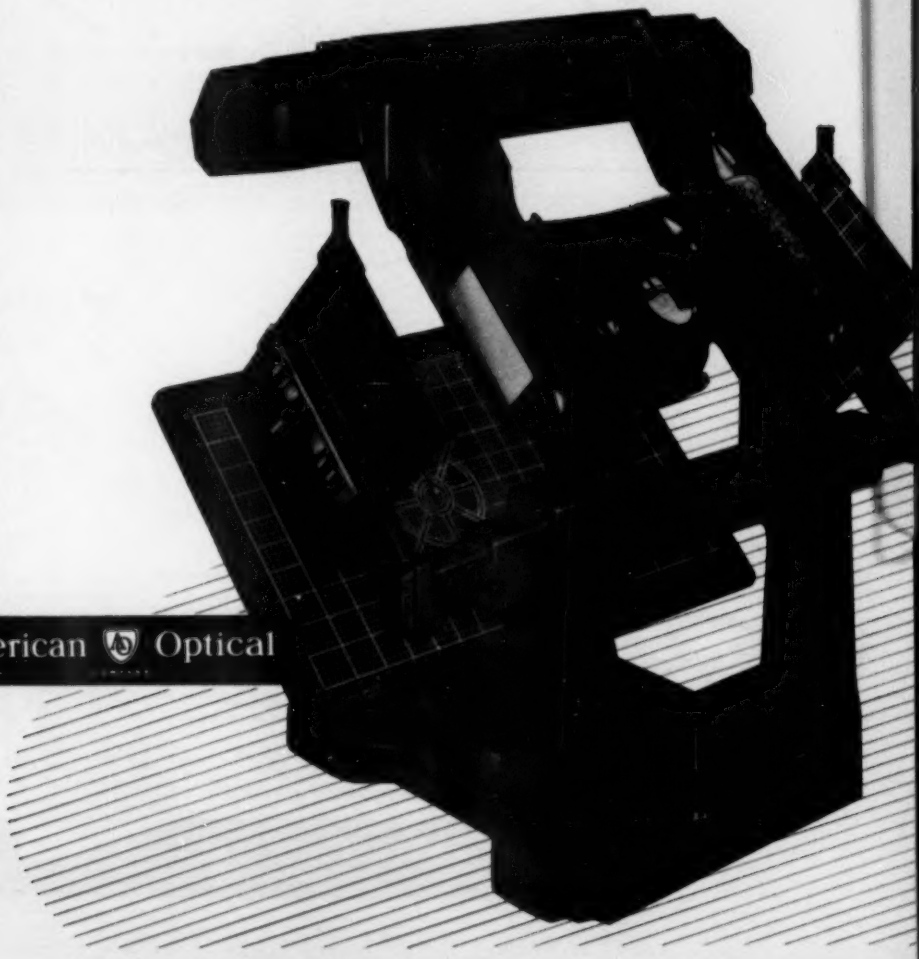

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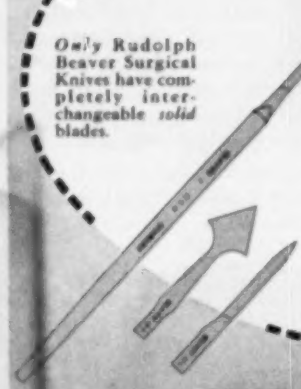

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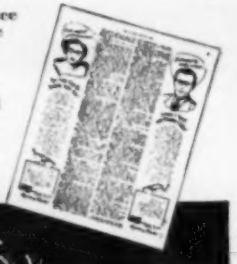

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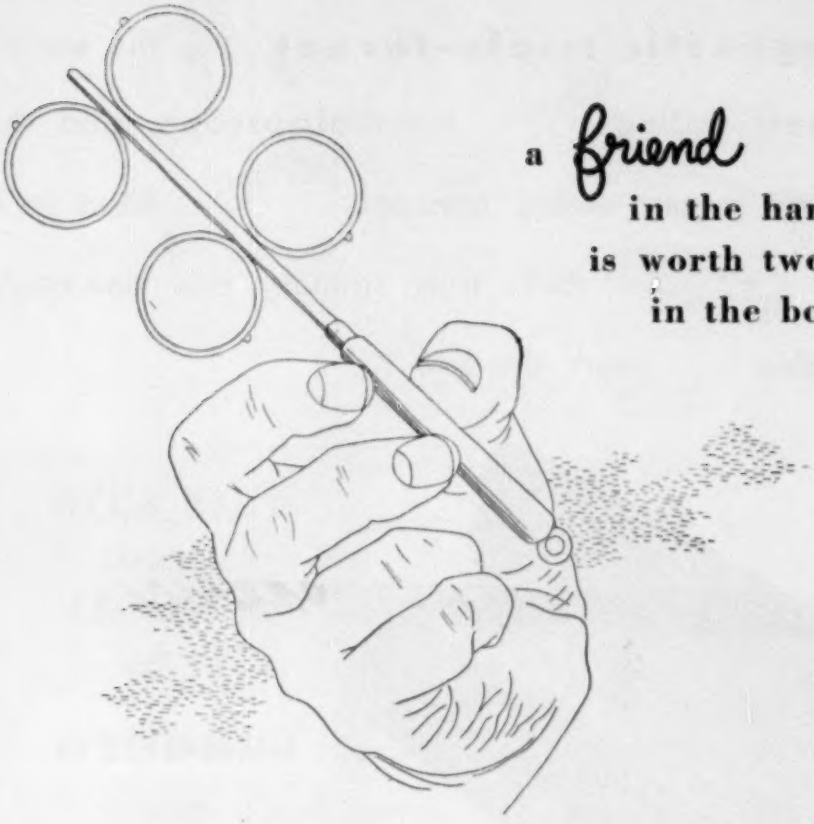

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ROLE OF THE ADRENAL CORTEX IN TREATMENT OF OCULAR DISEASES WITH PYROGENIC SUBSTANCES

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OPHTHALMOLOGISTS have long been impressed by the favorable, and frequently dramatic, immediate effects of general protein shock in diseases of the uveal tract. Nonspecific foreign protein shock therapy is now widely accepted in the management of acute and chronic inflammatory diseases of the eye. The agents producing more pronounced febrile reactions have gradually grown in popularity. Milk, milk derivatives and typhoid vaccine have enjoyed worldwide acceptance. Severe, and occasionally fatal, reactions to typhoid vaccine have led many physicians to prefer the milder-acting typhoid H antigen preparation.

An explanation of the specific therapeutic effect produced by these agents has been long in forthcoming. The concensus was that the severe general reaction, accompanied with leukocytosis, general and local vasodilatation, increased antibody titer, etc., stimulated the mechanism of immunity of the entire body to excessive response. It was not until 1946, when Selye[1] introduced his concept of the "general adaptation syndrome," that the underlying mechanism began to be understood. These agents appear to be "alarming stimuli," which evoke in the organism a "counter-shock phase," during which there exists increased resistance to any specific stress. Subsequent research dealing with the hormonal relationships of the hypothalamic-pituitary-adrenal axis has disclosed that such alarming stimuli indirectly activate the adrenal cortex.[2] This produces increased output of 11, 17-oxysteroids from the adrenal cortex. The increased resistance which occurs in the "counter-

From the Department of Ophthalmology, University Hospital.

1. Selye, H.: The General-Adaptation-Syndrome and the Disease of Adaptation, J. Clin. Endocrinol. 6:117, 1946.

2. Hume, D. M., and Wittenstein, G. J., in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 145.

shock phase" is largely dependent on the release of these 11, 17-oxysteroids from the adrenal cortex. Removal of the adrenal glands renders an animal susceptible to fatal injury from stresses which would be insignificant to a normal animal, and, conversely, the ability to withstand injuries is at least in part restored when an adrenalectomized animal is given a potent adrenal cortex extract in sufficient amounts. More recent observations of the action of the pituitary adrenocorticotropic hormone (ACTH) in ophthalmic disease states indicate that most dramatic results may occur in the acute phases of certain pathologic processes of the uveal tract. Careful clinical study further indicates that such responses simulate in most aspects those encountered in the alarm reaction.

We have long been interested in the basic response of the ocular tissues to general protein shock. In 1942 an attempt was made to substantiate Brown and Pugh's [3] thesis that increased antibody titer was produced in the aqueous by the administration of typhoid H antigen. Despite the use of massive doses, no rise in titer could be exhibited in either human blood or the aqueous of the rabbit. Recent reports have indicated that the eosinophil count is a delicate and fairly specific indicator of the response of the adrenal cortex to administration of ACTH.[4] In this paper we intend to examine the response of the eosinophil count to the administration of typhoid H antigen in the treatment of ocular disease in order to see whether the effects of protein therapy depend on the release of 11, 17-oxysteroids from the adrenal cortex.

METHOD OF STUDY

Eosinophils were counted by the method of Randolph.[5] Peripheral blood obtained by a finger prick giving a free blood flow was found to be as accurate, within the range of technical error, as was intravenous oxalated blood. All counts were made in duplicate, and the method was found to be satisfactory both as to convenience and as to reliability. Controls of normal patients received intravenous injections of isotonic sodium chloride solution and showed no significant decrease in eosinophil count.

For the last few years in this clinic the pyrogen in vogue has been the typhoid H antigen. This antigen has been found to give a fairly consistent response in terms of fever, malaise and improvement in ocular disease, and at no time has it been found seriously to endanger the patient. It has been the policy to begin treatment with from 15,000,000 to 25,000,000 units and to increase this dose by

3. Brown, A. L., and Pugh, J.: Effect of Intra-Ocular Concentration of Typhoid Antibodies on Experimental Corneal Ulcers, with a Report of 7 Cases, Arch. Ophth. **16**:476 (Sept.) 1936.

4. Forsham, P. H., in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 21.

5. Randolph, T. G.: Differentiation and Enumeration of Eosinophiles in the Counting Chamber with a Glycol Stain: A Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696, 1949.

10,000,000 to 20,000,000 units every other day, depending on the symptomatic and objective responses of the patient. The same procedure has been followed in the present study so that an evaluation of the existing method of fever therapy would be available.

In a case in which the patient was seriously refractory to typhoid H antigen a specific purified protein derived from the Shigella subgroup [6] was used. Except for the much smaller quantities used, the procedure in this case followed that for the typhoid H antigen.

The febrile response was graded in fever units. One fever unit represents 1 degree of temperature over 100 F. for one hour. All temperatures were oral temperatures, unless otherwise noted, and were recorded generally every hour while the temperature was rising and every two hours while the temperature was returning to normal. The degree of response, evaluated in units from 0 to 4 plus, represented an increasingly severe response in terms of general reaction. In accordance with accepted methods of typhoid therapy, injections were not given until the temperature had returned to normal.

RESULTS

Physiologically the autonomic nervous system is stimulated, causing a vascular dilatation in the splanchnic area with compensatory vasoconstriction peripherally, producing the chill. Shortly thereafter the peripheral vessels dilate as the body acts to lower the inner temperature.

It has been shown [7] that the peripheral vasoconstriction is the interference in the heat loss mechanism and is important in the production of a pyrogen fever. The heat production, which is correlated with the rise in temperature, is a consequence of the fever. With the rise in temperature there is a general stimulation of cellular activity, as shown by changes in the blood. At first there is a short period of leukopenia, followed by leukocytosis. The latter is accompanied with increased power of phagocytosis, increased antibody titer in the blood, rise in the blood content of proteolytic and lipolytic enzymes and increased permeability of capillary walls.[8]

The above data show correlation of eosinopenia, fever and general response when typhoid H antigen is used intravenously. It is believed that the eosinophil response is the most sensitive that one can get in terms of adrenocortical activation. The two tables present data on patients showing excellent eosinopenic response and those giving a poor response. It will be noted that eosinopenia and adrenocortical function are generally related directly to the degree of fever and malaise. However, apparent exceptions in this relationship can be explained by the variables in the time of taking the blood sample, tolerance to the type

6. Morgan, H. R.: Tolerance of Toxic Action of Somatic Antigens of Enteric Bacteria, J. Immunol. **59**:129, 1948.

7. Wells, J. A., and Rall, D. P.: Mechanism of Pyrogen Induced Fever, Proc. Soc. Exper. Biol. & Med. **68**:42, 1948.

8. Sanders, T. E.: Nonspecific Protein Therapy in Ocular Disease, J. Iowa M. Soc. **31**:51, 1941.

TABLE 1.—*Data on Patients Showing Good Eosinopenic Response to Typhoid H Antigen*

Case No.	Diagnosis	First Day: Eosinophil Count	First Day: Dose of Typhoid H Antigen, Millions of Units	First Day: Eosinophil Count	First Day: % Decrease*	First Day: Fever Units	First Day: Response	Second Day: Dose of Typhoid H Antigen, Millions of Units	Second Day: Eosinophil Count	Second Day: % Decrease*	Second Day: Fever Units	Second Day: Response	Third Day: Dose of Typhoid H Antigen, Millions of Units	Third Day: Eosinophil Count	Third Day: % Decrease*	Third Day: Fever Units	Third Day: Response	Fourth Day: Dose of Typhoid H Antigen, Millions of Units	Fourth Day: Eosinophil Count	Fourth Day: % Decrease	Fourth Day: Fever Units	Fourth Day: Response	Final State After Therapy
1	Acute iritis (O. D.)	145	20	6	96	8	+ 3	None	121	..	..	....	60	13	91	6	+ 1	None	44	..	..	+ 1	Improved
2	Acute iritis (O. S.)	110	20	0	100	10	+ 3	None	61	..	..	....	35	11	80	8	+ 3	None	22	..	..	....	Improved
3	Acute iritis (O. D.)	110	40	5.5	95	4	+ 2	None	44	..	..	....	90	44	0	5	+ 2	None	55	..	..	....	Improved
4	Acute iritis (O. D.)	150	15	22	85	8	+ 3	None	200	..	..	....	70	25	84	10	+ 3	30	22	..	8	....	Worse
5	Acute iritis (O. S.)	150	10	33	78	4	0	25	0	100	7	+ 3	None	120	..	..	+ 1	25	122	0	5	+ 1	Worse
6	Acute iritis (O. U.)	198	15	5.5	97	6	+ 2	.....	Referred to local doctor	..	..	....	.....	..	..	..	....	.....	..	..	..	....	Improved
7	Chronic iridocyclitis (O. D.)	165	18	5.5	97	6	+ 1	None	156	..	..	....	50	0	100	5	+ 1	.....	..	..	..	....	Improved
8	Acute choroiditis (O. D.)	148	20	11	93	7	+ 2	None	132	..	..	....	40	0	100	10	+ 2	None	200	..	..	....	Improved
9	Corneal ulcer (O. S.)	194	15	28	81	0	+ 1	None	80	..	..	....	25	5.5	94.5	1	+ 2	None	80	..	..	....	Improved
10	Interstitial keratitis	143	15	0	100	10	+ 3	None	231	..	..	....	25	11	95	22	+ 2	None	44	..	..	....	Improved
11	Dendritic ulcer	110	15	16.5	85	5	+ 2	Treatment discontinued because of chest discomfort—eye better															Improved
12	Acute primary glaucoma	88	10	0	100	3	+ 1	None	140	..	..	....	None	134	..	..	....	70	11	92	3	+ 1	Improved
13	Papilledema (O. S.)	305	20	44	86	7	+ 3	75	0	200	12	+ 3	.....	..	..	..	....	.....	..	..	..	....	Improved
14	Chronic trachoma	72	20	5.5	92.5	0.5	+ 2	None	44	..	..	....	None	165	..	..	....	40	22	67	10	+ 2	No change
15	Chronic iridocyclitis	176	15	55	69	4	+ 2	None	352	..	..	....	80	35	85	2	....	None	350	..	..	....	Improved

* Mean percentage decrease 90, 24+ hours after injection

TABLE 2.—*Data on Patients Showing Poor Eosinopenic Responses to Pyrogens*

			First Day					Second Day					Third Day					Fourth Day					
Case No.	Diagnosis	Eosinophil Count	Dose of Typhoid H Antigen, Millions of Units	Eosinophil Count	% Decrease*	Fever Units	Response	Dose of Typhoid H Antigen, Millions of Units	Eosinophil Count	% Decrease*	Fever Units	Response	Dose of Typhoid H Antigen, Millions of Units	Eosinophil Count	% Decrease*	Fever Units	Response	Dose of Typhoid H Antigen, Millions of Units	Eosinophil Count	% Decrease*	Fever Units	Response	Final State of Disease After Therapy
1	Acute iritis (O. D.)	264	15	106	62.5	3.5	+ 1	None	143	..	..	.....	.....	..	..	..	Sigmoid resection	.....	..	..	..	..	Improved
2	Lacerated cornea (O. S.)	121	15	132	0	..	0	None	220	..	..	.....	50	11	95	2	+ 2	50	330 (eye healed)	0	..	..	Improved
3	Optic neuritis (O. S.)	264	15	154	42	3	+ 1	None	132	..	..	.....	50	143	0	2	.....	None	198	..	..	..	Improved
3	Optic neuritis (O. D.)	308	55	220	28.6	5	0	50	148	50	.	.....	50	160	0	4	+ 1	None	160	0	2	0	Worse
3	Optic neuritis (O. D.)	260	3 Shigella†	220	15	14	+ 2	3 Shigella†	98	60	..	+ 2	Later, 101	60	77	9	+ 3	.....	..	..	..	..	Improved
4	Old intraocular foreign body	286	20	165	42	1	+ 3	None	297	..	..	.....	50	132	55	11	+ 3	None	176	..	..	..	No change
5	Lid plastic post surgery	66	15	50	24	1	+ 1	None	150	..	..	.....	40	132	12	..	.....	65	176	0	..	..	No change
6	Old intraocular foreign body	99	15	165	0	6	+ 2	None	66	60	..	.....	35	99	0	2	+ 1	None	121	..	..	..	No change

* Mean percentage decrease in eosinophils 22, 24 hours after operation, 4 mg. of ACTH being equivalent to a 50 per cent eosinophil decrease in 4 hours and 35 mg. of ACTH to a 75 per cent eosinophil decrease in 4 hours.

† A purified protein extract of a Shigella subgroup, the dose being expressed in micrograms.

of foreign protein used and poor adrenal function. Failure of improvement in the disease following an initially good adrenocortical reaction is best explained at present by an inhibition of the hypothalamic-pituitary axis by the abnormally high titer of 11, 17-oxysteroids. The mean percentage decrease in eosinophils of 93 in the first table is equivalent to about 100 mg. of ACTH, while the corresponding value of only 26 per cent in the second table represents about 2 mg. of ACTH. This poor adrenocortical reaction in the second group can probably be interpreted as relative insensitivity of the axis systems to stimuli and is best exemplified by case 3 of that group. The patient responded poorly to typhoid H antigen, so a purified protein extract of the Shigella subgroup was used. When tolerance to the new protein was also demonstrated, it was believed to be an illustration of the nonspecificity of the tolerance development. However, adequate doses of the new pyrogen finally gave excellent results. The phenomenon of tolerance, or refractoriness, is usually defined as a rapid loss of responsiveness to the pyrogen with continued therapy. Elevation of temperature is not necessary to its development, but when tolerance is reached further pyrogen therapy produces no further adrenocortical stimulation.

COMMENT

At present, there are two general approaches to the treatment of disease. The first, specific etiological therapy, has reached its height in the chemotherapy of infectious disease. The second approach depends on increasing the resistance of the host to his disease and is most clearly exemplified by treatment with ACTH or cortisone (17-hydroxy-11-dehydrocorticosterone). The present data clearly indicate that successful foreign protein therapy of ocular disease likewise involves the release of 11, 17-oxysteroids from the adrenal cortex. The effective duration of a treatment parallels the duration of eosinopenia, a specific response to 11, 17-oxysteroids. Moreover, patients in whom the stress of foreign protein injection fails to produce eosinopenia do not show a therapeutic response to this agent.

The two known effective stimuli for the release of increased amounts of ACTH and 11, 17-oxysteroids are epinephrine and a decrease in the circulating corticoid level. Epinephrine apparently acts by releasing a hormone from the hypothalamis which stimulates the anterior lobe of the pituitary; this hormone, in turn, releases ACTH from the pituitary gland, and the response to a decrease in the circulating corticoid level probably also involves this pathway. It is not known whether or not foreign protein therapy acts through one of these two mechanisms and stimulates the hypothalamic center indirectly, or whether it is a direct hypothalamic stimulating agent. It is interesting, however, to note

that the vasomotor and temperature-regulating centers, which are prominently affected by foreign protein treatment, are in close proximity in the hypothalamus to the center controlling the rate of release of ACTH from the anterior lobe of the pituitary.

As compared with ACTH or cortisone therapy, foreign protein therapy has both advantages and disadvantages. The most obvious advantage is its low cost, while the major disadvantage is the rapid development of tolerance to its effect. Often tolerance is apparent by the time the fourth injection has been given, and this refractory state may not be overcome by changing the pyrogenic agent.[9] A similar tolerance limits the usefulness of repeated doses of epinephrine as an agent for releasing ACTH, apparently because increased levels of 11, 17-oxysteroids inhibit the reaction of the hypothalamopituitary mechanism to stimulating agents. Previously it was believed that the functional capacity of the reticuloendothelial system to remove the bacterial toxins from the blood was enhanced by repeated injections of pyrogenic substances. This increased ability then afforded protection to the susceptible tissues, so that the latter were less damaged; and the fever response, which is probably a reflection of tissue injury, was accordingly decreased with each dose.[10] Pyrogenic protein therapy, however, appears superior to the use epinephrine, which has only a brief duration of action. In these studies maximum stimulation of the adrenal cortex following the administration of typhoid H antigen was not reached for 18 hours, and single doses appeared to have a duration of action of approximately 24 hours.

Neither the present results nor any data in the literature yet provide a satisfactory explanation of how adrenal steroids relieve ocular disease, or any other type of disease. For the present, it must be admitted that we are treating diseases of unknown origin with agents whose site of action is unknown.

The present results suggest that typhoid H antigen therapy has a definite, continuing place in the treatment of ocular disease. It should be most effective in those conditions which may be controlled by an elevation of the 11, 17-oxysteroid level for one week or less. Recently foreign protein has also been found effective as a supplementary therapeutic agent after withdrawal of a patient from ACTH therapy. When patients become refractory before their disease is controlled, when a

9. Beeson, P. B.: Tolerance to Bacterial Pyrogens: Factors Influencing Its Development, J. Exper. Med. **86**:29, 1947. Kapuscinski, W. J., Jr.: Pyrétothérapie comme provocation diagnostique dans les uvéites, Arch. d'opht. **1**:27, 1949.

10. Beeson, P. B.: Tolerance to Bacterial Pyrogens: Role of Retculo-Endothelial System, J. Exper. Med. **86**:39, 1947.

prolonged course of treatment will clearly be necessary and when patients fail to show an eosinopenic response to adequate doses, the use of ACTH or cortisone should replace foreign protein treatment.

SUMMARY

1. The intravenous injection of foreign protein initiates an alarm reaction with subsequent response of the adrenal steroids, as shown by a decrease in the eosinophils in the circulating blood.

2. The point of maximal eosinopenia is about 18 hours after the injection.

3. Eosinophil counts can be used to determine the time for the next injection.

4. Patients refractory to foreign protein show no decrease in eosinophils.

5. As evidenced by the eosinopenia, the adrenocortical response parallels the general constitutional reaction to the foreign protein.

Dr. James T. McGuckin, of the Department of Ophthalmology of the University Hospital, assisted in accumulating a part of the data; Dr. Herbert Morgan, of the Department of Medicine of the University of Rochester School of Medicine and Dentistry, donated the purified protein derived from the Shigella organism for the treatment of one of the highly refractory patients who is included in this report.

HEREDITARY NUCLEAR CATARACT

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AND
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IN 1947 a young girl and her brother came to one of us (Benedict) for treatment of bilateral cataract. Both patients had had the cataracts since early childhood, and their condition had remained stationary. Although visual efficiency was impaired, especially in bright light, both children had progressed excellently in school and were not obviously handicapped. The cataracts were central only, the nucleus of the lens being clearly outlined as a gray disk and the periphery of the lens being clear. The children's mother had undergone needling for bilateral cataract in childhood, with somewhat disappointing results. The children's aunt exhibited the same gray nuclear cataracts without gross visual difficulty. Three years previously, in 1944, this aunt had brought her two sons (cousins of the children described above) to one of us (Benedict) for treatment, and their clinical records contained a description of bilateral nuclear cataract corresponding exactly with that of their cousins.

Here, then, were six blood relatives, five with the same type of nuclear cataract and the sixth with a history of having undergone an operation for cataract. A brief inquiry into the pedigree revealed numerous other relatives with "bad eyes," all of whom were direct descendants of one man. The pedigree was worked out in greater detail by correspondence during the following months.

In 1948 a trip was undertaken to examine the eyes of as many members of this family as possible. The results of this trip formed the basis for a thesis, namely, the presentation of a new pedigree of hereditary nuclear cataract. This paper is a condensation of that thesis.

---

* Dr. Benedict is in the Section on Ophthalmology, Mayo Clinic.

Read at the meeting of the Texas State Medical Association, San Antonio, Texas, May 2 to 5, 1950.

This paper is an abridgment of a thesis submitted by Dr. Lee to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Ophthalmology.

The type of cataract encountered here was first studied and described in the literature by Nettleship and Ogilvie [1] in 1906. They published the pedigree of the Coppock family, of which 18 members were "known to be affected by a very definite and peculiar variety of stationary congenital cataract." Doyne [2] had encountered and described the first three or four cases in 1888, 1895 and 1896. Ogilvie discovered most of the others, and the first published pedigree contained 288 affected members in seven generations.

Subsequent pedigrees were published by Nettleship [3] (1908 and 1909), Chance [4] (1907), Harman [5] (1909 and 1910) and Smith [6] (1910). The cataract became known as "the Coppock cataract," or "Doyne's discoid cataract." Vogt [7] (1922) and Gifford [8] (1924) independently described the appearance of the cataract as seen with the slit lamp. Vogt termed it "central pulverulent cataract," but Gifford recognized the fact that the central pulverulent cataract of Vogt and the Coppock cataract of Nettleship and Ogilvie were identical. Adams [9] (1942) and Rosen [10] (1945) further described the appearance of the cataract with the slit lamp. In their textbooks Duke-Elder,[11] Mann [12] and Bellows [13] briefly mention the condition.

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1. Nettleship, E., and Ogilvie, F. M.: A Peculiar Form of Hereditary Congenital Cataract, Tr. Ophth. Soc. U. Kingdom **26**:191-207, 1906.

2. Doyne, R. W., cited by Nettleship and Ogilvie.[1]

3. Nettleship, E.: Lamellar Cataract, "Coppock" or Discoid Cataract, and Retinitis Pigmentosa, Affecting Different Members of the Same Pedigree, Tr. Ophth. Soc. U. Kingdom **28**:226-247, 1908; On Some Hereditary Diseases of the Eye, ibid. **29**:lvii-cxcvii, 1909.

4. Chance, B.: An Unusual Form of Hereditary Congenital Cataract Occurring in Several Members of a Family, Arch. Ophth. **36**:505-508, 1907.

5. Harman, N. B.: Congenital Cataract: A Pedigree of 5 Generations, Tr. Ophth. Soc. U. Kingdom **29**:101-108, 1909; Familial Discoid or "Coppock" Cataract, ibid. **30**:29-30, 1910.

6. Smith, P.: A Pedigree of Doyne's Discoid Cataract, Tr. Ophth. Soc. U. Kingdom **30**:37-42, 1910.

7. Vogt, A., cited by Rados, A.: Central Pulverulent (Discoid) Cataract and Its Hereditary Transmission, Arch. Ophth. **38**:57-77 (July) 1947, p. 62.

8. Gifford, S. R.: Congenital Anomalies of the Lens as Seen with the Slit Lamp, Am. J. Ophth. **7**:678-685 (Sept.) 1924.

9. Adams, P. H.: Doyne's Discoid Cataract (Coppock), Brit. J. Ophth. **26**:152-153 (April) 1942.

10. Rosen, E.: Coppock Cataract and Cataracta Pulverulenta Centralis, Brit. J. Ophth. **29**:641-644 (Dec.) 1945.

11. Duke-Elder, W. S.: Text-Book of Ophthalmology: Volume 1: The Development, Form and Function of the Visual Apparatus, St. Louis, C. V. Mosby Company, 1933.

12. Mann, I.: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937.

13. Bellows, J. G.: Cataract and Anomalies of the Lens: Growth, Structure, Composition, Metabolism, Disorders and Treatment of the Crystalline Lens, St. Louis, C. V. Mosby Company, 1944.

Rados [14] in 1947 published a most thorough report on central pulverulent cataract. He reviewed the literature extensively, and he himself reported on three new families which had the cataract. He further demonstrated that the mode of inheritance is dominant, that recessive inheritance of the condition cannot be substantiated and that the cataract does not show changes of transmission.

PRESENT STUDY

With the two children referred to as propositi, their pedigree was charted, and as many persons as possible were examined. In the new pedigree there were 200 members, in six generations; 63 inherited the family eye condition, 129 were unaffected and the condition of 8 was unknown (fig. 1).

The pedigree goes back to a man who was born in Ireland and who moved to South Carolina, probably about 1830. He raised eight children, four of whom are said to have had poor eyes; but the descendants of only the sixth child have been traced. This sixth child was born in 1835, in South Carolina; moved to Cropwell, Ala., and later moved to Texas. He died in Texas in 1900. Most of his descendants now live in Texas and Oklahoma.

One hundred and five persons were examined; 42 of these exhibited the cataract, and 63 presented clear lenses. Of the 95 not examined, 21 were said to have the "bad eyes" of the family, and 66 were said to have "good eyes." In most cases this information was checked and confirmed by several close relatives. The remaining eight persons died too early in infancy for other members of the family to know whether or not the eyes were affected.

The oldest affected person examined was 84 years of age, and the youngest was 3 months. With the exception of the 3 month old baby, all the affected members exhibited the same type of nuclear cataract, some of the cataracts being denser than others.

The hereditary nuclear cataract found in this new pedigree adhered to the mendelian law of dominance. Every affected person had an affected parent, and in no case had an unaffected person transmitted the condition. An affected person had usually transmitted the cataract to roughly one-half his children. The characteristic was not sex linked; there were 34 affected males and 29 affected females, figures that are within the limits of probability for even distribution. In one instance there were fraternal twins, one of whom was affected and the other unaffected. There were no instances of intermarriage between affected persons.

14. Rados, A.: Central Pulverulent (Discoid) Cataract and Its Hereditary Transmission, Arch. Ophth. **38**:57-77 (July) 1947.

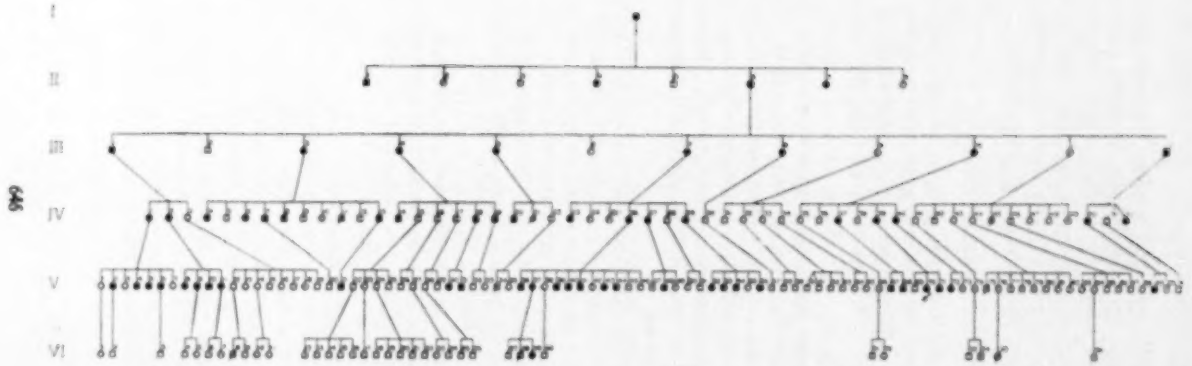

Fig. 1.—Of 200 members in six generations, 63 were affected, 129 were unaffected and 8 were not traced. In this pedigree chart, clear squares indicate normal males; clear circles, normal females and black squares or circles, affected males or females.

Most members of this family appeared to be above average intelligence, and a number of them were quite definitely superior. In no case was there any mental deficiency. The average educational level was just short of high school graduation, being almost the same for the persons with cataract as for those without it. With two exceptions, the presence of cataract did not prevent any one from starting school, although several did leave in the lower grades. Many with cataracts, however, made exceptional academic records; at least two were class valedictorians.

Although the cataract apparently remains stationary throughout life, visual acuity neither improving nor decreasing, the parents were usually

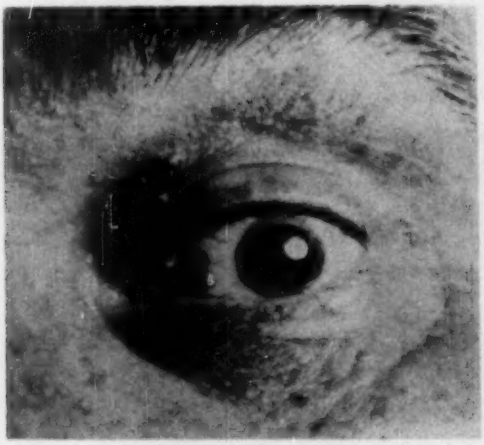

Fig. 2.—Typical hereditary nuclear cataract. The white spot over the pupil is a light reflex from the cornea.

not aware that a child had the family cataract until the child was about 2 years of age, and evidence of its presence might not be definite until about the age of 4. Each member of the family and those who married into it were conscious of this hereditary trait, and they were anxious to know as soon as possible whether or not a baby was affected. If a child had the cataract, the first ocular symptom or sign was preference for shade, rather than bright light. This might manifest itself by the child's squinting in the light, tilting or cocking his head to avoid the light or preferring to play in subdued light or dark corners, closets and indoors. But during the first two years of life the child normally exhibited no such objection to light. This aversion to bright light carried through

adult life. Because the cataract was central, constriction of the pupil to light impaired vision.

The nuclear cataracts were always sharply circumscribed; and, with one exception, they could be cataloged in one of the three varieties originally described by Nettleship and Ogilvie, namely: (1) dense gray, (2) thin gray and (3) granularly opaque (fig. 2). Many showed a distinct triradiate structure, with a clear Y on the anterior aspect of

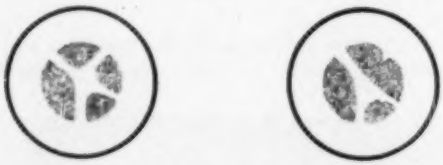

Fig. 3.—Distribution of opacities in the lens, showing a distinct triradiate structure with a clear Y on the anterior aspect of the opacity.

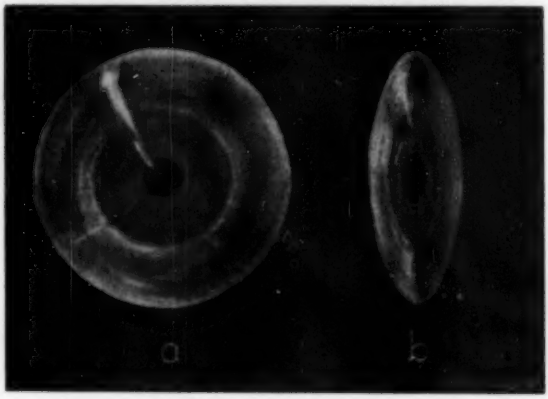

Fig. 4.—Hereditary nuclear cataract in a child 3 months old.

the opacity (fig. 3). This frequent appearance of the Y, together with the fact that the opacities were usually 4 to 4.5 mm. in diameter, would seem to point to the fetal nucleus, rather than simply to the embryonic nucleus, as the zone of pathological change.

The one person whose cataracts differed significantly from the others was the 3 month old baby (fig. 4). The Y sutures were clearly visible as broad, clear lines continuous with the periphery of the lens; through these lines of the Y could be seen the red fundus reflex. In the nuclear areas formed by the angles of the Y were thin dark, homo-

geneous opacities, through which the fundus reflex could not be seen. At first glance these opacities appeared to be scattered rather haphazardly in the lens, but a second inspection proved that such was not the case. The exact center of the lens was clear but was surrounded by a circle of broad, thin opacities separated from each other by only the Y suture. The peripheral edge of each opacity was part of a circle, the complete, circumscribed circle being made up of all the opacities and measuring 6 to 7 mm. in diameter (fig. 5). The parents had noticed nothing wrong with the baby's visual behavior and did not suspect that the child had cataracts.

The findings in this 3 month old baby, together with the fact that symptoms of cataract usually do not appear in affected persons until about the age of 2 years, suggest the probability that central pulverulent

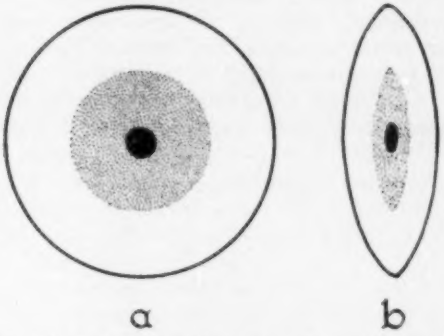

Fig. 5.—Distribution of opacities in a hereditary nuclear cataract.

cataract is not formed in the embryonic nucleus but involves only the fetal nucleus. The findings further suggest the possibility that, although the cataract is present at birth, it does not reach its final, stationary phase until about the age of 2 years. It will be important to reexamine this child at a later date to observe whether her cataract has assumed the form of others.

SUMMARY

A new pedigree of hereditary nuclear cataract is presented. Of 200 members, in six generations, 63 were affected, 129 were unaffected, and the condition of 8 was unknown. One hundred and five of these persons were examined personally, 42 exhibiting the cataract and 63 having normal eyes. Information regarding the 95 members not examined was obtained from close relatives and was usually confirmed by others.

This cataract was first described in 1906 by Nettleship and Ogilvie, and it has subsequently been termed by other observers "the Coppock cataract," "Doyne's discoid cataract" and "central pulverulent cataract." It is strictly a dominant hereditary characteristic, and it is not sex linked.

It is probable that the cataract involves only the fetal nucleus, and that the embryonic nucleus is primarily not affected. It would seem that the cataract does not reach its final stage of development and become stationary until about the age of 2 years.

STUDIES ON THE CRYSTALLINE LENS

III. Incorporation of Glycine and Serine in the Proteins of Lenses Cultured in Vitro

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AND
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PREVIOUS experiments [1] with lenses cultured in vitro with labeled glycine have shown that the tripeptide glutathione turns over continuously, being degraded into its component amino acids and resynthesized at similar rates. A significant amount of labeled glycine in these experiments was also found in the lens proteins. The present study is concerned with whether the lens proteins are similarly in a state of flux and whether interconversions of amino acids occur in the lens.

No previous studies of the interconversions of amino acids and the turnover of lens proteins have been made, nor had a detailed analysis of the amino acid composition of lens proteins been reported at the time these studies were performed.[2] There has been a recent investigation, however, on the oxidative metabolism of amino acids. De Vincentiis and Auricchio [3] demonstrated the ability of the lens to oxidize several amino acids to keto acids, which, in turn, are oxidized further. This oxidation illustrates one path for catabolic degradation of the amino acids

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This work was supported in part by a grant from the United States Atomic Energy Commission.

1. (*a*) Merriam, F. C., and Kinsey, V. E.: Studies on the Crystalline Lens: I. Technic for in Vitro Culture of Crystalline Lenses and Obesrvations on Metabolism of the Lens, Arch. Ophth. **43**:979 (June) 1950. (*b*) Kinsey, V. E., and Merriam, F. C.: Studies on the Crystalline Lens: II. Synthesis of Glutathione in the Normal and Cataractous Rabbit Lens, ibid. **44**:370 (Sept.) 1950.

2. After completion of these studies, a report on the amino acid composition of bovine lens proteins was made by A. J. Schaeffer and J. D. Murray (Amino Acid Composition of the Lens Proteins of the Bovine Eye, Arch. Ophth. **43**:1056 [June] 1950). They used a microbiological procedure, and their results are in substantial agreement with ours, although they did not report ammonia.

3. de Vincentiis, M., and Auricchio, G.: Sur le metabolisme des acides aminés dans les tissus oculaires, Acta ophth. **28**:7, 1950.

in the lens and, since the concentration of amino acids remains essentially constant, suggests that they are turning over as they do in other tissues.[4]

To test whether the lens proteins are in a state of flux with regard to the component amino acids, lenses were incubated in vitro with glycine labeled in either the carboxyl or the methylene position with C^{14}. The protein was hydrolyzed, and the component amino acids were separated by means of starch column chromatography.[5] Then, by determining the radioactivity in each fraction, it was possible to determine the fate of the C^{14} from the labeled glycine. An analysis of the acid-hydrolyzed lens proteins was obtained at the same time.

METHODS

Two pairs of lenses from albino rabbits 4 to 6 weeks old were cultured by the procedure described in a previous paper,[1a] using solution 2. This basic culture medium was fortified with labeled glycine in the following way: A 10.5 ml. portion of the culture solution was labeled with 95.2 microliters of a stock solution of methylene-labeled glycine containing 3.75 mg. (0.05 millicurie) per milliliter, or, in the second experiment, with 142.8 microliters of a solution of 3.0 mg. (0.04 millicurie) of carboxyl-labeled glycine per milliliter. All solutions were maintained sterile. Lenses were cultured for about 25 hours at 37 C. with 5.0 ml. each of the culture medium in an atmosphere of 5 per cent carbon dioxide, 5 per cent oxygen and 90 per cent nitrogen.

After culture, each lens was weighed, extracted twice by being ground in a glass mortar with 10 ml. portions of a 1 per cent aqueous solution of trinitrophenol to remove all the unbound amino acids, including glycine, then extracted with two 10 ml. portions of water and dried. The protein was then suspended in 10 ml. of water, and the amount of radioactivity was estimated by plating a 25 microliter aliquot of the protein suspension on a copper planchet. When dry, the C^{14} was counted directly, as were aliquots of solutions in the glutathione experiments.[1b]

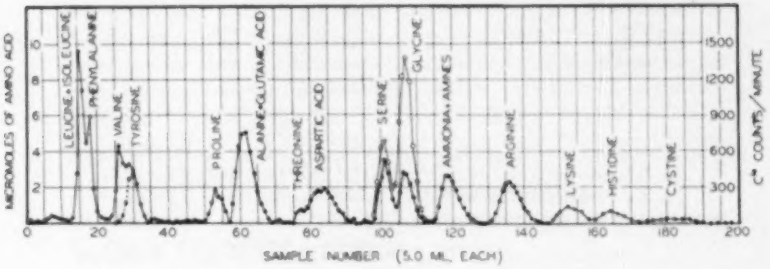
In order to remove lipids, a 25.3 mg. aliquot of vacuum-dried protein from one of the lenses was extracted twice with a 50: 50 alcohol-ether solution at the boiling point for 15 minutes. No radioactivity was found in the extract; so it appeared unlikely that glycine was extensively converted to the lipid fraction. The protein was again dried in a vacuum desiccator; then, for hydrolysis, it was transferred to a 200 by 14 mm. (outer diameter) pyrex® tube and suspended in 5 ml. of 5 N glass-distilled hydrochloric acid. The suspension was heated nearly to boiling to remove air; then the tube was sealed while still hot. The protein was hydrolyzed in a steam autoclave at a gage pressure of 20 pounds per square inch for 19 hours in the first experiment and for five hours in the second experiment. The solution was transferred to a 50 ml. Erlenmeyer flask, frozen in solid carbon dioxide and alcohol and evaporated to dryness at less than 1 mm. of mercury pressure. The autoclave tube was rinsed with about 4 ml. of water, which was added to the amino acid residue; the solution was again frozen and lyophilized to sweep out remaining hydrochloric acid.

4. Borsook, H.; Deasy, C. L.; Haagen-Smit, A. J.; Keighley, G., and Lowy, P. H.: Uptake of Labeled Amino Acids by Tissue Proteins in Vitro, Federation Proc. **8**:589, 1949.

5. Moore, S., and Stein, W. H.: Chromatography of Amino Acids on Starch Columns: Solvent Mixtures for the Fractionation of Protein Hydrolysates, J. Biol. Chem. **178**:53, 1949.

The solid residue of amino acid hydrochlorides was dissolved in 2 ml. of a 1:2:1 mixture of n-butyl alcohol, n-propyl alcohol and 0.1 N hydrochloric acid and introduced on the top of a 2.1 by 30 cm. starch column, which had been prepared by the procedure described by Stein and Moore.[6]

The elution of the amino acids from the potato starch was carried out with the same 1:2:1 mixture on a Technicon Automatic Fraction Collector. Five milliliter fractions were collected (245 drops) in tubes coated with a silicone film to prevent creeping. On the third day of operation, when aspartic acid was emerging from the column, the eluting mixture was changed to a 2:1 n-propyl alcohol–0.5 N hydrochloric acid solution to speed the rate of travel of the amino acids remaining on the column. Two hundred fractions were collected altogether. A 261 microliter aliquot of each fraction was analyzed for its leucine equivalent of amino acid content with triketohydrindene hydrate (ninhydrin®) by the procedure of Moore and Stein.[7] Ammonia and the 18 amino acids considered in this work give varying amounts of color with ninhydrin®; so it was necessary to correct the color yield for the efficiency of color formation with each amino acid. Our correction factors were in substantial agreement with those found by Moore



Separation of the amino acids from hydrolyzed rabbits lens proteins by starch column chromatography. The line with closed circles represents the amount of amino acid present; the line with open circles, the amount of C^{14} present.

and Stein. The amount of amino acid in each fraction was calculated, using the appropriate correction factors. To determine the amount of C^{14} in the fractions, they were lyophilized and plated on copper planchets and counted by the usual procedure.

RESULTS

The amount of amino acid present in each chromatogram sample, as well as the amount of C^{14} present, is plotted as a function of the sample number (and hence as a function of eluate volume, since each sample was 5.0 ml.) in the accompanying chart. By adding the amount of a given amino acid in each of the samples comprising the peak for this

6. Stein, W. H., and Moore, S.: Chromatography of Amino Acids on Starch Columns: Separation of Phenylalanine, Leucine, Isoleucine, Methionine, Tyrosine, and Valine, J. Biol. Chem. **176**:337, 1948.

7. Moore, S., and Stein, W. H.: Photometric Ninhydrin Method for Use in the Chromatography of Amino Acids, J. Biol. Chem. **176**:367, 1948.

amino acid, it was possible to determine the amino acid content in the sample placed on the column. These integrated values for the experi-

TABLE 1.—*Amino Acid Composition and C^{14} Distribution in Lens Proteins Following Incubation of a Four Week Old Rabbit Lens for Twenty-Five Hours in the Presence of Glycine Labeled with C^{14} in the Methylene Position*

Amino Acid	Amino Acid, Micromoles	Percentage (On a Molecular Basis)	C^{14} Counts/Min.
Leucine-isoleucine	18.43	10.4	±
Phenylalanine	11.15	6.3	±
Valine-methionine	8.04	4.9	±
Tyrosine	9.22	5.1	±
Proline	9.55	5.4	±
Alanine-glutamic acid	25.00	14.0	..
Threonine	4.42	2.3	..
Aspartic acid	14.00	8.2	..
Serine	10.63	6.0	2,450
Glycine	13.73	7.7	6,580
Ammonia	25.57	14.3	..
Arginine	13.01	7.3	..
Lysine	5.77	3.2	±
Histidine	5.88	3.3	..
Cystine (½)	1.54	0.9	..
	178.06	100.1	

TABLE 2.—*Amino Acid Composition and C^{14} Distribution in Lens Proteins Following Incubation of a Six Week Old Rabbit Lens for Twenty-Five Hours in the Presence of Glycine Labeled with C^{14} in the Carboxyl Position*

Amino Acid	Amino Acid, Micromoles	Percentage (On a Molecular Basis)	C^{14} Counts/Min.
Leucine-isoleucine	22.40	12.3	..
Phenylalanine	11.05	6.4	..
Valine-methionine	12.80	7.0	..
Tyrosine	10.08	5.8	..
Proline	7.45	4.1	±
Alanine-glutamic acid	28.90	15.8	..
Threonine	4.02	2.2	..
Aspartic acid	13.68	7.5	..
Serine	12.88	7.0	2,465
Glycine	12.80	7.0	6,495
Ammonia	16.10	8.8	±
Arginine	15.58	8.5	..
Lysine	6.60	2.7	..
Histidine	5.60	3.1	..
Cystine (½)	1.58	0.9	..
	180.01	100.1	

ments are presented in tables 1 and 2, along with the protein composition which was calculated from these values. The protein composition is expressed as a percentage based on the number of molecules of each amino acid present, because in protein studies the relative number of amino acid units is more informative than the relative weights of

the amino acids. It will be observed that the major portion of the labeled glycine was found in the glycine and serine portion of the protein.

In cases in which the peaks overlapped, the amino acids were estimated by the procedure recommended by Stein and Moore,[8] with the exception of valine, methionine and tyrosine. Tyrosine was determined directly in the appropriate fractions by comparing the absorption at 276 millimicrons with that of standard tyrosine solutions. When the peak representing the difference between the tyrosine peak and the combined valine, methionine and tyrosine peaks was plotted separately, a smooth, symmetrical curve was obtained. This indicates that the amount of methionine, which usually appears between valine and tyrosine in this type of chromatogram, was very small in these acid hydrolysates of lens proteins. Hence only valine is indicated in the chart, although a little methionine may also be present.

No values are reported for tryptophan in the chart and tables, because this amino acid is destroyed by an acid hydrolysis of the type used in these experiments.[5] The glycine and ammonia peaks represent slightly more material than that in peptides, because the acid hydrolysis breaks down adenine and guanine in nucleic acids to glycine and ammonia.[6] This effect must be small, however, because the nucleic acid content of the lens is not over 0.15 per cent of the lens proteins.[9] A more serious error in this type of analysis is the destruction of cystine during hydrolysis.[10] The extent of loss is not known at present.

With these exceptions, the analysis presented accounts for over 98 per cent of the amino acids of the lens proteins.

COMMENT

The results of these experiments strongly suggest that there is a turnover of glycine in lens proteins. However, it has been pointed out elsewhere [4] that experiments on the incorporation of labeled amino acids into tissue protein must be interpreted with caution when pure proteins cannot readily be isolated, since there are other ways in which an amino acid may be associated with protein than in peptide bonds. For example, in liver homogenates glycine may be incorporated into glutathione, which, in turn is linked through its sulfur atom to the sulfur of protein. Glycine may also be incorporated into phospholipids, which are difficult to separate from the protein, or it may be bound to the protein by a complex

8. Markham, R., and Smith, J. D.: A Source of Error in Amino Acid Analysis, Nature, London **164**:1052, 1949.

9. Mandel, P.; Nordman, J., and Zimmer, J.: Acide nucléique du cristallin, Compt. rend. Acad. sc. **228**:516, 1949.

10. von der Becke, C. H.: Perdidas de cisterina durante la hidrolisis acida de proteinas, Semana méd. **57**:115, 1950.

with a heavy metal. The possibility of incorporation of glycine in protein by means other than peptide bond replacement in these experiments was eliminated in the following way:

After lenses were incubated with carboxyl-labeled glycine, extraction of the dry lens proteins with hot ether and alcohol removed less than 1 per cent of the C^{14}; thus, it is unlikely that C^{14} was present in the phospholipids. Treatment of the same lens proteins directly with ninhydrin* liberated less than 1 per cent of the C^{14} as carbon dioxide. Since this reagent is specific for alpha-amino carboxyl groups, it would react with free glycine or glycine loosely bound in a complex. The absence of any reaction suggests that glycine is bound to protein by peptide bonds. Finally, a partial solution of the radioactive lens proteins in 3 N thioglycolic acid for six hours at 30 C. failed to alter appreciably either the specific activity of the soluble portion, which was precipitated with 2.5 N sodium hydroxide at p_H 5, or the specific activity of the protein insoluble in the reagent. Thioglycolic acid has been used by others [11] to remove cystine and peptides bound to protein by a disulfide link. In the case of liver homogenates, a considerable amount of C^{14} from glycine is removed from protein in this way,[12] while C^{14} in the same proteins after incubation with labeled phenylalanine is not.[10] The evidence presented here, therefore, indicates that incorporation of C^{14} from glycine takes place largely by replacement of glycine units in the lens peptide chains.

The large amount of C^{14} present in serine suggests a rather rapid conversion of glycine to serine in the lens. This interconversion in the lens is only a little slower than that in liver.[13]

The rate at which glycine enters and leaves the lens proteins can be estimated if certain assumptions are made concerning the size of the pool throughout which labeled glycine is distributed during a culture experiment. For example, it has already been shown [1b] that glycine in the culture medium mixes not only with the unbound glycine in the lens but also with the glycine in glutathione. Now, it has been shown that there is potentially a large amount of glycine in the lens proteins which could increase the size of the pool considerably and, in fact, would do so in an experiment of, say, a week's duration. Furthermore, if serine is considered to be in equilibrium with glycine, the pool becomes even larger.

11. Melchior, J. B., and Tarver, H.: Studies in Protein Synthesis in Vitro: I. On the Synthesis of Labeled Cystine (S^{35}) and Its Attempted Use as a Tool in the Study of Protein Synthesis, Arch. Biochem. **12**:301, 1947.

12. Peterson, E. A.; Greenberg, D. M., and Winnick, T.: Characteristics of the Amino Acid Incorporation System of Liver Homogenates, Federation Proc. **9**: 214, 1950.

13. Goldsworthy, P. D.; Winnick, T., and Greenberg, D. M.: Distribution of C^{14} in Glycine and Serine of Liver Protein Following the Administration of Labeled Glycine, J. Biol. Chem. **180**:341, 1949.

In the absence of information on the rate at which serine is converted to glycine and formate, the turnover rate for glycine in protein can be obtained only within limits. These limits are established by making the assumption that no conversion to glycine takes place or that this conversion is infinitely rapid.

If no conversion of serine to glycine occurs, then the total pool in which C^{14} would be distributed at isotopic exchange equilibrium consists in the glycine fed, the unbound glycine in the lens, the glycine in glutathione and the glycine in the lens proteins. In the case of a lens in the experiment with methylene-labeled glycine, these values were 0.170, 0.014, 0.108 and 2.224 mg., respectively, and the total pool was 2.516 mg. of glycine. The amount of C^{14} which could be distributed in the pool was the amount fed minus the amount which was lost in serine (and in carbon dioxide when carboxyl-labeled glycine was used), or $61.1 \times 10^4 - 0.5 \times 10^4$, or 60.6×10^4 counts per minute. The amount of C^{14} which would be in protein had isotopic equilibrium been reached during the culture period would be $60.6 \times 10^4 \times (2.224/2.516)$, or 53.7×10^4 counts per minute. The actual number of counts per minute found to be present in protein glycine after 25 hours was 1.42×10^4. Thus, the turnover was $100\% \times 1.42 \times 10^4/53.7 \times 10^4$, or 2.6 per cent complete.

A similar value for the experiment with carboxyl-labeled glycine was a 2.7 per cent turnover in 25 hours.

If serine is converted to glycine infinitely rapidly, the pool of 2.516 mg. of glycine must include an additional 1.74 mg. of glycine which is potentially available from serine. Under these conditions, the amount of C^{14} which would be in protein glycine had isotopic equilibrium been reached during the culture period would be $(2.224/4.256) \times 61.1 \times 10^4$, or 32.0×10^4 counts per minute, and the glycine turnover in 25 hours would be 4.4 per cent. The corresponding value in the experiment with carboxyl-labeled glycine was 5.85 per cent.

By similar calculations, the over-all conversion of glycine to serine in protein was 2.1 and 2.3 per cent in 25 hours for the experiments with methylene-labeled and carboxyl-labeled glycine, respectively.

Within the limits defined above, it appears that the rate at which glycine molecules are replaced in the intact rabbit lens proteins was 2.5 to 5 per cent per day, while the serine was synthesized from glycine and replaced at the rate of about 2 per cent per day.

It is noteworthy that these turnover reactions did not take place when the lens capsule was removed or seriously damaged before the lens was cultured. Similar disturbances in the metabolism of the lens on rupture of the capsule have been observed by others. For example, it is known that removal of the capsule results in a twofold to fourfold increase in

oxygen uptake.[14] The possible relation between these metabolic disturbances will be discussed in a subsequent paper. When the lens capsule was removed after the lens was cultured with labeled glycine, only a small part of the C^{14} was lost, indicating that, while the intact capsule is necessary for glycine turnover, the turnover does not take place in the capsule alone.

While this paper has been limited to the turnover of glycine and serine in the lens proteins, it may be presumed from evidence available from studies on other tissues that most of the other amino acids behave similarly.

SUMMARY

Evidence is presented to show that the proteins of the lens are continuously being degraded and resynthesized.

Glycine labeled with C^{14} in the carboxyl or the methylene position was shown to turn over in rabbit lenses cultured in vitro at a rate between 2.5 and 5 per cent per day. This amino acid was also shown to be rapidly converted by the lens to serine, which, in turn, was incorporated into protein at a comparable rate.

The amino acid composition of young rabbit lenses as obtained by chromatographic analysis on acid-hydrolyzed proteins is presented.

Dr. Ivan D. Frantz Jr. made helpful suggestions, and Mrs. Ethel Bowie gave technical assistance.

14. Ely, L. O.: Metabolism of the Crystalline Lens: II. Respiration of the Intact Lens and Its Separated Parts, Am. J. Ophth. **32**:220, 1949.

METABOLISM OF THE STORED CORNEA

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SINCE preservation of the donor material is one of the most important problems facing the ophthalmologist who is actively engaged in doing corneal transplantations, several investigators [1] have studied the question from the clinical, histological and biochemical points of view. In a recent article, Duane [2] demonstrated that the oxygen uptake of the cornea remains normal for about seven days when the eye is stored in a moist chamber in the refrigerator. Preliminary experiments [3] conducted in this laboratory showed that when the enucleated eyeball is stored in a moist chamber in the refrigerator, the procedure employed by Duane,[2] and also the method employed nowadays in most of the eye banks in this country, the cornea rapidly takes up water. Of course, the abnormal hydration will change the corneal architecture and will cause histological and biochemical changes. It is obvious that the excessive water which diffuses into the cornea during the storage process must come from the

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1. Castroviejo, R.: Present Status of Keratoplasty, Arch. Ophth. **22**:114 (July) 1939. Thomas, J. W. T.: Experimental Transplantation of Cornea, Tr. Am. Ophth. Soc. **51**:88, 1931. Katzin, H. M., and Kno, P. H.: Histologic Study of Experimental Corneal Transplantation, Am. J. Ophth. **31**:171, 1948. Leopold, I. H., and Adler, F. H.: Use of Frozen-Dried Cornea as Transplant Material, Arch. Ophth. **37**:268 (March) 1947. Scherschewskaya, O. J.: Keratoplastische Versuche mit Anwendung von Formolloppen, Ophthalmologica **99**:4, 1940. Shestericova, T., and Rosenfeld, E.: Respiration of the Cornea During Preservation, Ukrain. Biochem. J. **18**:201, 1946.

2. Duane, T. D.: The Respiration of the Stored Cornea, Am. J. Ophth. **31**: 1400, 1948.

3. At the nineteenth annual meeting of the Association for Research in Ophthalmology, held in San Francisco, June 24 and 25, 1950, before this investigation was completed, Buschke reported that the cornea stored in the conventional manner takes up water, whereas the excised cornea maintains its normal wet weight when stored in the refrigerator. The present investigation confirms Buschke's results.

rest of the eyeball. Therefore, to prevent this excessive hydration of the cornea during storage, and thereby preserve its metabolic activities in a more physiological state, it was decided to remove the cornea immediately after enucleation and store it in the refrigerator in the excised state. In an attempt to demonstrate that excised corneas maintain normal metabolic activity for a longer period than those stored in the conventional manner, the following experiment was carried out.

TECHNIC

Fresh beef corneas, received approximately three hours after the death of the animal, were used throughout this study. Two methods of preservation were employed: (1) The eyes were placed in a moist chamber which was saturated with 0.9 per cent sodium chloride solution and were stored in the refrigerator at 2 C. or (2) the corneas were excised and then stored in a moist chamber at 2 C. The oxygen uptake, the respiratory quotient and the glycolytic activity of the corneas were measured in the manner described in other communications.[4]

TABLE 1.—*Oxygen Uptake (Expressed in Microliters of Oxygen Absorbed per Milligram Dry Weight Tissue per Hour) of Bovine Corneas Following Preservation at 2 C., Both in the Excised and in the Intact State* [*]

Days of Storage	Excised Cornea			Intact Cornea		
3	−0.56	−0.61	−0.59	−0.55	−0.54	−0.64
4	−0.50	−0.45	−0.66	−0.65	−0.54	−0.51
6	−0.55	−0.50	−0.60	−0.62	−0.49	−0.55
8	−0.09	−0.07	−0.15	−0.63	−0.13	−0. 0
10	−0.59	−0.28	−0.45	−0.37	−0.35	−0.28
19	−0.40	−0. 0	−0.39	−0.19	−0. 0	−0.06

[*] Each figure represents one cornea.

For the carbohydrate and nonprotein nitrogen determinations, the corneas were divided with scissors into small fragments and extracted with 4 per cent trichloroacetic acid. To determine the carbohydrate content, the indole reaction, as described by Dische,[5] was employed; in this method fraction I contained the acid-soluble sugars, while fraction II included the protein-bound, alkali-soluble carbohydrates. The nonprotein nitrogen was determined with the conventional nesslerization procedure. One half of each cornea was used for analysis; the other half was dried to constant weight, and then all results were calculated in terms of dry weight.

RESULTS

For the sake of simplicity, the corneas stored according to the conventional method, i. e., on the intact globe, will be referred to as "intact"

4. deRoetth, A., Jr.: Respiration of the Cornea, Arch. Ophth., this issue, p. 666. Clycolytic Activity of the Cornea, to be published.

5. Dische, Z., and Popper, H.: Über eine neue kolorimetrische Mikrobestimmungsmethode der Kohlehydrate in Organen und Körpersaften, Biochem. Ztschr. **175**:371, 1926. Alexander, C., and Dische, Z.: Colorimetric Micromethod for the Determination of Sugars in Polysaccharides and Tissue Extracts, to be published.

corneas, while the others, which were stored in the excised state, will be referred to as "excised" corneas.

Table 1 shows that the oxygen uptake of the stored corneas, both the intact and the excised type, was normal for about six days, but after that time the results became erratic and inconsistent. Chart 1 demon-

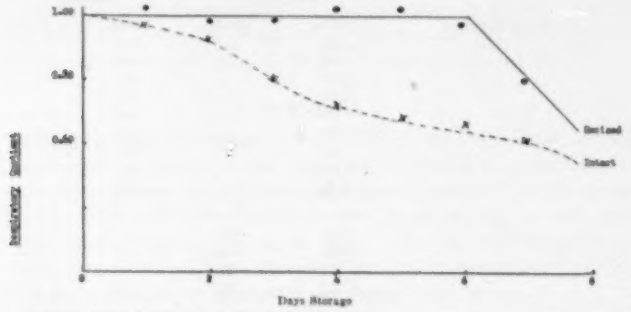

Chart 1.—Respiratory quotient of 56 bovine corneas after preservation at 2 C., both in the "intact" and in the excised state.

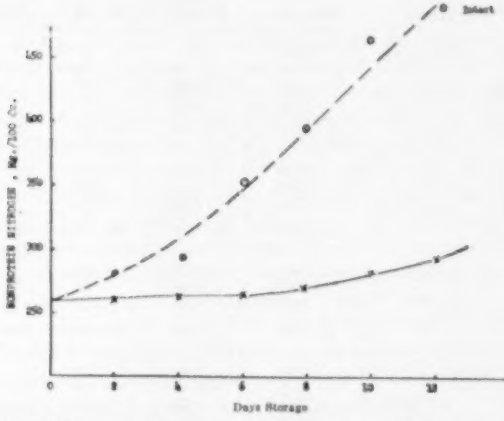

Chart 2.—Nonprotein nitrogen of 36 bovine corneas after preservation at 2 C., both in the "intact" and in the excised state.

strates that the respiratory quotient of the excised corneas remained normal for about six days, whereas that of the intact corneas started to fall below 1.00 after the first day of storage.

Table 2 represents the results of the studies of carbohydrate content. Although the individual variations were great, the total averages show

that the acid-soluble sugars (fraction I) tended to decrease in the excised corneas and to increase in the intact corneas. The protein-bound

TABLE 2.—*Carbohydrate Content of Fifty-One Bovine Corneas Following Preservation at 2 C., Both in the Intact and in the Excised State*

Days of Storage	Fraction I		Fraction II	
	Excised	Intact	Excised	Intact
0	0.322	.....	2.86	....
	0.260	.....	2.34	....
	0.298	.....	3.26	....
	0.339	.....	3.32	....
	0.475	.....	2.96	....
	0.403	.....	3.45	....
	0.444	.....	3.26	....
	0.450	.....	3.49	....
	Av. 0.296	.....	Av. 3.04	....
2	0.422	0.360	....	....
	0.322	0.330	3.17	3.08
	0.370	0.300	3.14	3.12
	Av. 0.379	Av. 0.360	Av. 3.16	Av. 3.07
4	0.300	0.408	....	2.98
	0.380	0.457	3.22	3.00
	0.297	0.474	3.09	3.15
	Av. 0.388	Av. 0.426	Av. 3.20	Av. 3.01
6	0.208	.....	....	....
	0.355	.....	3.00	2.98
	0.318	0.426	2.82	2.76
	0.344	0.438	3.74	2.68
	Av. 0.331	Av. 0.432	Av. 2.85	Av. 2.79
8	0.228	0.670	2.91	2.39
	0.281	0.507	2.78	2.58
	0.350	0.427	2.29	....
	Av. 0.286	Av. 0.468	Av. 2.66	Av. 2.43
10	0.308	0.314	3.25	2.85
	0.316	0.605	2.91	2.57
	0.236	0.484	2.72	2.43
	Av. 0.259	Av. 0.476	Av. 2.96	Av. 2.62
12	0.253	0.476	2.92	2.94
	0.316	0.522	3.10	2.51
	0.326	0.503	3.04	2.41
	Av. 0.298	Av. 0.500	Av. 3.02	Av. 2.62
Total average	0.330	0.445	2.97	2.75

* Fraction I comprises trichloroacetic acid-soluble sugars; fraction II, protein-bound, alkali-soluble carbohydrates.

sugars (fraction II), on the other hand, remained approximately normal in the excised corneas, but they decreased in the intact corneas.

Chart 2 demonstrates that in the excised cornea the nonprotein nitrogen remained normal for about six days and then slowly increased. In the intact cornea, however, the increase in the nonprotein nitrogen was striking, starting after the first day of storage.

The results of the glycolytic studies were inconclusive; both the aerobic and the anaerobic glycolytic activities of the stored corneas remained approximately normal for eight days, but the results were too variable to have any real significance. There was no appreciable difference between the excised and the intact corneas in this respect.

COMMENT

The oxygen uptake studies yielded little, if any, significant results. As mentioned previously, Duane [2] reported that the QO_2 (microliters of oxygen absorbed per milligram dry weight tissue per hour) of the cornea preserved under the conventional storage conditions of the eye bank remains normal for six to seven days. The present investigation confirms his results and also demonstrates that there is practically no difference in the QO_2 of the intact and the excised cornea.

The other experiments, however, yielded more interesting results. The respiratory quotient of the excised cornea remained normal for about six days, whereas that of the intact cornea started to fall below 1.00 after the first day. This finding agreed well with the results of the nonprotein nitrogen studies. In the excised cornea the nonprotein nitrogen remained normal for about six days, whereas in the intact cornea the nonprotein nitrogen started to rise rapidly after the first day. Thus, one can observe a close parallelism between the respiratory quotient and the nonprotein nitrogen; as long as there was no excess protein breakdown, the nonprotein nitrogen remained normal and the respiratory quotient was about 1.00, showing a normal carbohydrate metabolism. However, as soon as proteolysis began, the nonprotein nitrogen started to increase, concurrently with a lowering of the respiratory quotient, indicating a predominantly protein breakdown type of metabolism. Since this shift from a normal carbohydrate metabolism to an abnormal proteolysis occurred after the first day in the intact cornea and only after six days in the excised cornea, it can be assumed that in the excised state the cornea retained a more normal type of metabolism than in the intact condition when stored in a moist chamber at 2 C.

In table 2 each figure represents experiments using one cornea, these values being shown to illustrate the striking individual variation. Although this great variation makes one hesitate to draw any final conclusions from this experiment, certain facts, nevertheless, are obvious. It can be seen that the excised cornea tended to lose some of the trichloroacetic acid–extracted sugars during the storage period. The

loss in sugar content can be explained by a slow, yet appreciable metabolism which takes place in the excised cornea, even at 2 C., resulting in some breakdown of carbohydrate to supply the energy requirements. In the intact cornea, on the other hand, the trichloroacetic acid–soluble sugar increased during the storage period. A possible explanation is that during the process of hydration of these intact corneas, sugar, as well as water, was carried into the cornea, resulting in a progressive accumulation of acid-soluble carbohydrates. A different explanation for this increased sugar content can be arrived at if one examines the results of fraction II of the indole test, i. e., the protein-bound sugars. It can be seen that this fraction remains approximately normal in the excised cornea but decreases in the intact cornea. This breakdown of glucoprotein seems to fit with the rest of the picture. The protein fraction undergoes further disintegration, resulting in an increased nonprotein nitrogen and a lowering of the respiratory quotient, while the sugar fraction contributes to the gradual increase of the acid-soluble carbohydrate content of the intact cornea. This is further proof that during the storage period the metabolism of the excised cornea was maintained for a longer time than that of the intact cornea. Since the present study indicates that from the biochemical point of view it is more advantageous to store corneas in the excised than in the intact state, it would be interesting to investigate also the viability of the excised cornea and to compare it with that of the intact cornea.

A word of caution, however, should be expressed at this point. Corneas stored in the excised state are inconvenient to handle for transplantation purposes; it is difficult to cut out a disk with the trephine from such an excised cornea, because it is not supported *in situ* by the rest of the globe. Moreover, most surgeons use only 24 to 48 hour old donor material, during which time there is little, if any, difference in the metabolism of the excised and that of the intact corneas. Thus, it is not my purpose to advocate storage in the excised state as the method of choice for the preservation of corneal donor material; rather, I wish only to draw the attention of ophthalmologists to the fact that from the biochemical point of view the corneas remained normal for a longer period in the excised than in the intact state.

As stated previously, the glycolytic activities of these corneas stayed close to the normal range for at least eight days. Leinfelder [6] examined the aerobic glycolytic activity of "intact" bovine and rabbit corneas stored for one to four days in the refrigerator; he noted that, although most of the corneas showed a normal aerobic glycolysis, there was greater

6. Leinfelder, P. F.: Aerobic Glycolysis of Corneal Tissue, Tr. Am. Ophth. Soc. **46**:412, 1948.

variation in the rates of glycolysis for the bovine eyes. This striking variation in the appearance of the curves was also noticed in the present investigation, for both aerobic and anaerobic glycolysis. This means that the glycolytic activity of these corneas was disturbed only to a slight degree during the period of preservation.

SUMMARY

The metabolism of the cornea was studied under various storage conditions. Excised corneas were observed to maintain a normal carbohydrate breakdown for six days when stored in a moist chamber at 2 C.

"Intact" corneas, under similar storage conditions, showed evidences of protein breakdown after the first day of storage.

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RESPIRATION OF THE CORNEA

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THE RESPIRATORY activity of isolated surviving tissues has been extensively investigated in the last 25 years. The respiration of the cornea has also been studied, but, as compared with what is known of other tissues, knowledge concerning its metabolic activities is somewhat sketchy and confusing. The present study was undertaken in an attempt to fill in some of the gaps remaining in the present concept of corneal respiration and to help in clarifying some of the contradictory reports that have appeared in the literature.

I. RESPIRATION OF THE CORNEA IN AIR

The first question to be studied was: Can the cornea utilize oxygen from the surrounding atmosphere? Because of its unique position in the body, i. e., its being remote from the blood stream and exposed to the air, this question has interested many investigators. More than 50 years ago, in 1899, long before the Barcroft-Warburg manometric technic for the measurement of oxygen uptake was known, Bullot and Lor [1] transplanted eyes into peritoneal cavities and observed that the cornea could not survive under such low oxygen tension. Employing the same general principle, Gundersen [2] demonstrated that the cornea could not survive when transplanted into the anterior chamber. Fischer [3] fitted elaborately constructed glass chambers on eyes of living animals and then analyzed the gases formed in these vessels under various experimental conditions. Bakker [4] performed similar experiments,

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1. Bullot, G., and Lor, L.: De l'influence exercée par l'épithélium de la cornée sur l'endothelium et le tissu cornéens de l'œil transplanté, Bull. Acad. roy. de méd. de Belgique **13**:421, 1899.

2. Gundersen, T.: Results of Autotransplantation of Cornea, Tr. Am. Ophth. Soc. **36**:207, 1938.

3. Fischer, F. P.: Ueber den Gasaustausch der Hornhaut mit der Luft, Arch. f. Augenh. **102**:146, 1930.

4. Bakker, A.: Some Researches on the Respiration of the Cornea in Albino Rats, Brit. J. Ophth. **31**:100, 1947.

except that he placed the entire animal in the chamber. Their results were contradictory; Fischer stated that the cornea obtains its supply of oxygen from the air, the endothelium being responsible for the respiration of the cornea, while the epithelium acts only as a barrier to the gaseous exchange but itself does not respire. He also minimized the importance of the limbal blood vessels in the respiration of the cornea. Bakker, on the other hand, stated the belief that the cornea does not obtain its oxygen supply from the surrounding atmosphere; he stressed the significance of the limbal circulation. Because of these varying results, it was decided to reexamine this problem. Therefore, to demonstrate that the excised cornea can utilize atmospheric oxygen, the following experiment was carried out.

TECHNIC

Rabbit, cat and beef eyes were used; the beef eyes were obtained from freshly slaughtered young animals and reached the laboratory within approximately three hours after the death of the animal, the eyes being kept on ice during this time. The so-called direct Warburg manometric technic was employed to measure oxygen uptake. One beef cornea was placed on the bottom of each specially constructed Warburg flask, which had a circular, trough-shaped center well around the side of the vessel, thus leaving the bottom empty. The flask was large enough so that one beef cornea could be placed in it without folding. The endothelial side of the cornea rested on the bottom of the vessel, while the epithelial surface faced upward. No substrate was used in the main compartment of the flask; i. e., the cornea was placed dry in the flask, with its epithelial surface exposed to the air in the vessel. The center well contained 0.2 ml. of 10 per cent sodium hydroxide, and a small amount of 1/6 N sulfuric acid was placed in the side arms. This dilute acid served a twofold purpose: Being isotonic with the cornea, it prevented dehydration, and it absorbed any ammonia that might have been liberated from the cornea during the experiment. The flasks were incubated at 37 C., and the manometers were read at one-half hour intervals over a two hour period. The experiments were limited to two hours, because if they lasted longer than this one could not exclude the effects of bacterial contamination. The rabbit and cat corneas were handled in a similar manner, the only difference being that, because of their small size, two or three of them were placed in each flask. The gas phase in the flasks was either air or 100 per cent oxygen.

After the experiment the corneas were dried to constant weight at 105 C. The results were expressed in the conventional QO_2 units, i. e., microliters of oxygen absorbed per milligram dry weight cornea per hour.

To measure the respiratory quotient (R. Q.) of the cornea in the air, four similar flasks were used for each experiment, one quadrant from each of four beef corneas being placed in each flask. The first flask contained cornea, sodium hydroxide, for absorption of the carbon dioxide, and dilute sulfuric acid. The second flask was similar to the first except that it had water in its center well instead of alkali, and thus the carbon dioxide given off by the cornea was not absorbed. The third and fourth flasks contained corneal tissue plus 0.4 ml. of 50 per cent trichloroacetic acid in the side arm. In the third flask this acid was tipped into the main compartment at the beginning of the experiment, while in the fourth flask it was tipped in at the end of the experiment. Trichloroacetic acid

liberates carbon dioxide bound in the tissues; therefore in flask 3 I measured the amount of bound carbon dioxide that was present initially in the tissue, while in flask 4 I measured the initial carbon dioxide plus that produced during the course of the experiment but yet bound to the tissue. The difference between the readings in manometers 3 and 4 gave the amount of tissue-bound carbon dioxide liberated during the experimental period. After due corrections for unequal weights and tissue-bound carbon dioxide, the R. Q. $\left(\frac{\text{carbon dioxide produced}}{\text{oxygen consumed}}\right)$ was calculated as described by Umbreit and associates.[5]

RESULTS

Table 1 shows that the cat, rabbit and beef corneas respire in air, the average QO_2's being —0.34, —0.74 and —0.62, respectively. There was no difference in the QO_2 of the beef corneas whether the gas phase was 100 per cent oxygen or air. The average R. Q. for 48 beef corneas, including the tissue-bound carbon dioxide, was 1.00. Without the tissue-bound carbon dioxide, the average R. Q. of the cornea was 0.75, thus showing that 25 per cent of the respiratory carbon dioxide was retained by the tissue.

TABLE 1.—*Oxygen Uptake of Bovine, Rabbit and Cat Corneas, in QO_2 Units* *

	Beef			Rabbit	Cat
Gas phase	Air	Oxygen	Air	Air	Air
	—0.60	.....	....	.....	.....
	—0.61	.....	....	.....	.....
	—0.55	.....	....	.....	.....
	—0.54	.....	....	.....	.....
	—0.66	.....	....	.....	.....
	—0.62	.....	R. Q.†	—0.80	—0.36
	—0.68	.....	....	—0.82	—0.27
	—0.67	.....	1.00	—0.60	—0.27
	—0.62	.....	0.94	—0.68	—0.35
	—0.62	.....	0.98	—0.64	—0.30
	—0.64	—0.59	0.92	—0.79	—0.37
	—0.59	—0.61	1.00	—0.91	—0.34
	—0.57	—0.57	1.02	—0.80	—0.40
	—0.64	—0.56	0.90	—0.69	—0.39
	—0.61	—0.64	1.01	—0.65	—0.26
Average	—0.61	—0.60	1.00	—0.74	—0.34

* Microliters of oxygen absorbed per milligram dry weight tissue per hour, each figure representing one cornea.
† Respiratory quotient (R. Q.) of 32 bovine corneas, each figure representing four corneas.

The above experiment demonstrates that the excised surviving cornea takes up oxygen from the atmosphere, since the corneas were placed in the Warburg flasks dry, i. e., without any fluid in the main compartment of the vessel, and their epithelial surfaces were facing upward and thus exposed to the air in the flask. This does not prove

5. Umbreit, W. W.; Burris, R. H., and Stauffer, J. F.: Manometric Techniques and Tissue Metabolism, Minneapolis, Burgess Publishing Company, 1949.

that the cornea necessarily has to take up oxygen from the air; it means only that it can utilize atmospheric oxygen. It is probable that in the living animal the cornea obtains its oxygen supply both from the air and indirectly from the blood supply via the limbal vessels and the aqueous. Thus, during sleep, for example, when the lids cover the cornea, the oxygen supply must come from the limbal vessels and the aqueous; but when the lids are open oxygen can be taken up directly from the air.

An R. Q. of 1.00 indicates a predominantly carbohydrate metabolism. A review of the literature fails to reveal studies of the respiratory quotient of the cornea except those of Leinfelder.[6] He mentioned briefly that the R. Q. of the cornea is approximately 1 but did not describe the experimental procedure. It is essential to take into consideration the tissue-bound carbon dioxide, because without it the R. Q. would be only 0.75. As the experiment for determination of the respiratory quotient was also conducted with the cornea in the "dry state," i. e., without any fluid in the main compartment of the vessels, it is obvious that the cornea, besides absorbing oxygen from the air, can also give off carbon dioxide directly to the atmosphere. The studies of Herrmann and associates,[7] Friedenwald [8] and Duane [9] indicate that the cornea has a predominantly carbohydrate type of metabolism. The direct measurement of the R. Q. of the surviving cornea, as I have demonstrated, supports this contention.

At this time it should be mentioned that several investigators measured the oxygen consumption of the surviving cornea at 37 C. for six to eight hours. According to present concepts, the disturbing effect of bacterial contamination cannot be excluded under such experimental conditions. Herrmann and Hickman,[10] for example, reported that after incubating corneas at 32 to 34 C. for 10 to 20 hours bacterial growth was usually not visible with the naked eye. However, beginning bacterial growth can occur long before it becomes grossly visible and thus might interfere with the respiratory activity of the tissue. Therefore, to exclude the possibility of bacterial contamination interfering with

6. Leinfelder, P. J.: Aerobic Glycolysis of Corneal Tissue, Tr. Am. Ophth. Soc. **46**:412, 1948.

7. Herrmann, H.; Moses, S. G., and Friedenwald, J. S.: Influence of Pontocaine Hydrochloride and Chlorobutanol on Respiration and Glycolysis of Cornea, Arch. Ophth. **28**:652 (Oct.) 1942.

8. Friedenwald, J. S.: Studies on the Physiology, Biochemistry, and Cytopathology of the Cornea in Relation to Injury by Mustard Gas and Allied Toxic Agents: XVII. Summary and Some Possible Interpretations, Bull. Johns Hopkins Hosp. **82**:326, 1948.

9. Duane, T. D.: Metabolism of the Cornea, Arch. Ophth. **41**:736 (June) 1949.

10. Herrmann, H., and Hickman, F. H.: Exploratory Studies on Corneal Metabolism, Bull. Johns Hopkins Hosp. **82**:225, 1948.

the experiment, it was decided to limit the length of oxygen uptake measurements to a few hours only, when experiments were conducted at body temperature.

II. EFFECT OF p_H AND COMPOSITION OF THE SUSPENSION MEDIUM ON CORNEAL RESPIRATION

Duane's [9] excellent review demonstrates that the oxygen uptake of the excised cornea is not a constant value; the QO_2 measurements of the cornea reported by the various authors show great individual variations. Therefore an attempt was made to find a reason for these variations and to standardize the experimental conditions under which oxygen uptake is measured.

The most important factor to be studied is the p_H of the medium in which the cornea is suspended during the experiments. Most of the previous investigators employed a phosphate-buffered Ringer's solution with 0.2 per cent dextrose, p_H 7.2 to 7.4. It is well known that phosphate is not a physiological buffer, and there are several reports in the literature concerning its inhibitory action on tissue respiration (Dische [11]; Ashwell and Dische [12]). The tissue proteins, on the other hand, are considered excellent physiological buffers. In this respect the cornea offers interesting possibilities, since the proteins and mucoproteins of the relatively inactive corneal stroma could be considered as adequate buffering systems already provided by nature. Therefore, it was assumed that because of the buffering capacity of the corneal stroma, which exceeds in bulk the metabolically active epithelium, the p_H of the suspension medium will have little, if any, effect on the respiratory activity of the cornea. To test the validity of this assumption, the following experiment was carried out.

TECHNIC

Into each special flat bottom Warburg flask was placed one fresh beef cornea, cut into quadrants. The suspension medium was plain Ringer's solution, Ringer's solution with a 0.2 per cent dextrose or a phosphate-buffered (p_H 7.3), balanced salt solution containing NaCL, KCL, KH_2PO_4, $MgSO_4$ and $NaHCO_3$, as described by Krebs.[13] One hundred per cent oxygen or air was used as the gas phase in the flasks, the carbon dioxide being absorbed by sodium hydroxide in the center well, and readings were taken over a two hour period at 37 C. In another series of experiments, the p_H was carefully adjusted with a Beckman glass electrode by adding small amounts of $NaHCO_3$ to Ringer's solution, the p_H range varying from 5.7 to 7.5.

11. Dische, Z.: The Aerobic Glycolysis of Avian Red Blood Cells and Its Control by Intracellular Ions in Physiological Concentrations, J. Biol. Chem. **163**:575, 1946.

12. Ashwell, G., and Dische, Z.: Inhibition of the Metabolism of Nucleated Red Cells by Intracellular Ions and Its Relation to Intracellular Structural Factors, Acta biochim. et biophys. **4**:276, 1950.

13. Krebs, H. A.: Body Size and Tissue Respiration, Acta biochim. et biophys. **4**:249, 1950.

RESULTS

Tables 2 and 3 show that the QO_2 of beef corneas does not depend on the composition or p_H of the suspending medium; within a p_H range

TABLE 2.—*Oxygen Uptake of Bovine Corneas, Expressed in QO_2 Units,* in Phosphate Buffer, Ringer's Solution and Ringer-Dextrose Solution*

Suspension medium	Phosphate Buffer		Ringer's Solution	Ringer-Dextrose Solution
Gas phase	Air	Oxygen	Air	Air
	−0.51	−0.55	−0.49	.....
	−0.59	−0.55	−0.54	.....
	−0.52	−0.52	−0.52	.....
	−0.54	−0.50	−0.56	.....
	−0.60	−0.56	−0.51	.....
	−0.58	−0.57	−0.50	−0.52
	−0.56	−0.54	−0.50	−0.58
	−0.52	−0.63	−0.47	−0.53
	−0.57	−0.62	−0.52	−0.48
	−0.56	−0.62	−0.55	−0.58
	−0.52	−0.59	−0.57	−0.52
	−0.54	−0.57	−0.50	−0.49
	−0.58	−0.68	−0.46	−0.44
	−0.53	−0.64	−0.51	−0.46
	−0.58	−0.61	−0.55	−0.55
Average	−0.55	−0.60	−0.52	−0.51

* Microliters of oxygen absorbed per milligram dry weight tissue per hour, each figure representing one cornea.

TABLE 3.—*Oxygen Uptake of Bovine Corneas, in QO_2 Units,* with Varying p_H of the Suspension Fluid*

p_H	QO_2
5.7	−0.55
5.9	−0.54
6.9	−0.56
6.7	−0.55
7.1	−0.52
7.2	−0.57
7.3	−0.56
7.5	−0.57
Average	−0.55

* Microliters of oxygen absorbed per milligram dry weight tissue per hour, each figure representing the average of two corneas.

of 5.7 to 7.5, the QO_2 of beef corneas was approximately the same, the average being —0.55. The average QO_2 for beef corneas in phosphate-buffered saline solution, Ringer's solution or Ringer-dextrose solution varied from —0.50 to —0.60. The gas phase was either 100 per cent oxygen or air and did not seem to affect the oxygen uptake.

COMMENT

The literature dealing with the advantages and disadvantages of various suspending mediums for studies of oxygen uptake is voluminous. According to present day concepts, one cannot make generalizations concerning the treatment of all tissues, for each tissue has its peculiarities and should be handled accordingly. In this respect the cornea holds a unique position; its rate of oxygen uptake is apparently entirely independent of both the composition of the suspending medium and the gas phase. Since the buffering capacity of proteins and mucoproteins is well known, one can assume that the large bulk of relatively inactive corneal stroma protects the metabolically active epithelium from any changes in the p_H of the surrounding medium. This experiment actually proved more than it was intended to; the QO_2 of the cornea remained normal not only in an unbuffered medium, such as Ringer's solution, but even when the medium was buffered with $NaHCO_3$ and the p_H was lowered purposely to 5.7. This shows that the buffering ability of the cornea could overcome the buffering capacity of the suspension medium.

On comparison of the figures of table 1 with those of tables 2 and 3, it may be noted that the cornea respires at the same rate in the presence and in the absence of a suspending medium.

If the results of this study are compared with the reports of previous investigators, as compiled by Duane,[9] it is seen that they agree with the findings of recent investigators, i. e., Herrmann,[14] Lee and Hart[14] and Robbie and associates.[14] The older investigators, on the other hand, reported entirely different results. Since the manometric technic was in its infancy when Kohra[14] and Fischer[14] made their oxygen uptake measurements, it is understandable that they obtained somewhat variable and contradictory results.

EFFECT OF HOMOGENIZATION ON THE OXYGEN UPTAKE OF THE CORNEAL EPITHELIUM

Another factor of importance in the study of tissue respiration is the physical treatment of the tissue. In order to supply the cells satisfactorily with oxygen and substrates, the tissue has to be sliced, minced, chopped or homogenized. The commonly accepted method is either to slice the tissue into very thin sections—the optimum thickness being 0.55 mm. (Fuhrman and Field[15])—or to homogenize it into a finely dispersed suspension. The cornea, because of its unique anatomic position and shape, resembles a tissue slice in its natural state. Since it is

14. Cited by Duane.

15. Fuhrman, F. A., and Field, J.: Factors Determining the Metabolic Rate of Excised Liver Tissue, Arch. Biochem. **6**:337, 1945.

well known that the major part of the metabolic activity of the cornea is carried out by the epithelium, which is only a fraction of a millimeter in thickness, it is not necessary to section the cornea further. Thus, nature conveniently provides a tissue that comes "pre-sliced," so to speak; this furnishes one with an excellent opportunity to study the effect of homogenization on the respiratory activity of the cornea.

TECHNIC

The corneal epithelium of fresh beef eyes was scraped off with a scalpel, and the weighed tissue was pooled and homogenized in a Potter-Elvehjem [16] ground glass tube attached to an electric motor. Krebs's [13] medium IIa, without the organic acids, was used to wash down the homogenate. Aliquot portions were then pipetted into Warburg flasks and diluted with the aforementioned buffered salt solution in such a fashion that each vessel contained approximately 400 mg. of

TABLE 4.—*Oxygen Uptake of the Homogenized Epithelium of Bovine Corneas, Expressed in QO_2 Units* Following the Addition of Dextrose, Pyruvate and Fumarate in Final Concentrations of 100, 10 and 25 Mg. per 100 Cc., Respectively*

Experiment	Control	Dextrose, 100 Mg./100 Cc.	Pyruvate, 10 Mg./100 Cc.	Fumarate, 25 Mg./100 Cc.
1 (15 corneas)	−0.51	.....	.....	.....
	−0.52	.....	.....	.....
2 (30 corneas)	−0.86	−0.87	−1.18	−1.23
3 (12 corneas)	−0.60	.....	−0.89	−0.93

* Microliters of oxygen absorbed per milligram dry weight tissue per hour.

fresh weight tissue. For calculation of the QO_2 the dry weight was estimated to be 20 per cent of the wet weight. Oxygen uptake was measured according to the direct Warburg method at 37 C. over a two hour period; dextrose, lithium pyruvate and sodium fumarate were added in physiological concentrations. These metabolites were employed in the present study, because it is known that they increase the oxygen consumption of most mammalian tissues. As a control experiment, the oxygen uptake of the remaining corneal stroma and endothelium was also measured, both in Krebs's [13] medium IIa and also in dry state, i. e., without any fluid in the main compartment of the flask. In a few corneas the QO_2 of the stroma alone was measured, after both the epithelium and the endothelium were scraped off. Oxygen uptake was calculated always from the steepest slope of the activity-time curve.

RESULTS

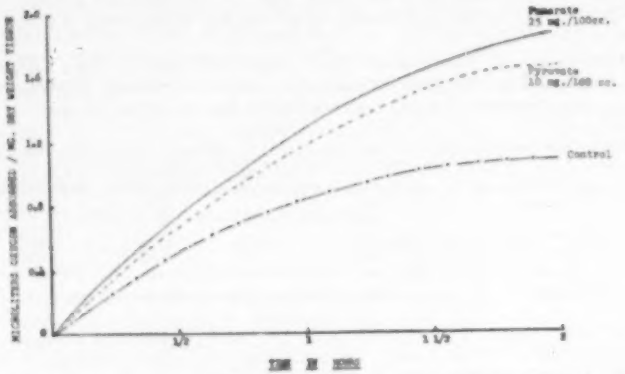
Table 4 shows that the QO_2 of the homogenized corneal epithelium is low—or about the same as that of the whole cornea. The additional pyruvate and fumarate increased the oxygen uptake, while dextrose had no effect. The remaining endothelium and stroma (table 5) showed a QO_2 about one fourth that of the whole cornea, while the stroma alone

16. Potter, V., and Elvehjem, C. A.: A Modified Method for the Study of Tissue Oxidations, J. Biol. Chem. **114**:495, 1936.

TABLE 5.—*Oxygen Uptake of the Various Layers of Bovine Cornea, in QO_2 Units**

	Endothelium and Stroma		Stroma Alone
Suspension medium	Phosphate Buffer	Dry	Phosphate Buffer
Gas phase	Air	Air	Air
	−0.150	−0.105	.....
	−0.216	−0.124	.....
	−0.130	−0.127	.....
	−0.181	−0.114	−0.092
	−0.169	−0.124	−0.093
	−0.197	−0.101	−0.092
Average	−0.164	−0.116	−0.093

* Microliters of oxygen absorbed per milligram dry weight tissue per hour.



Rate of oxygen uptake of the homogenized corneal epithelium of 50 bovine eyes following the addition of pyruvate and fumarate in final concentrations of 10 and 25 mg. per 100 cc., respectively.

had a barely perceptible respiratory activity. The chart demonstrates that the oxygen uptake of the homogenized epithelium fell off rapidly after the first 30 minutes, but the addition of pyruvate and fumarate maintained a higher and steadier rate of respiration for 1 to 2 hours.

COMMENT

The reports in the literature concerning the metabolic activities of the corneal stroma are contradictory. Some authors (Kohra,[14] Fischer,[14] Lee and Hart,[14] Robbie and associates [14] maintained that the stroma has a measurable respiratory activity; others (Orzalesi,[14] Herrmann [14] and others) have denied it. The present investigation demonstrates that the excised corneal stroma does take up oxygen.

The corneal epithelium being estimated as about one seventh the weight of the whole beef cornea (Herrmann and Hickman [10]), and the

QO_2 of the stroma (table 5) being only one fourth of the total cornea, the QO_2 of the epithelium is calculated to be about — 5.5, theoretically. This is about ten times the actual value measured for the homogenized epithelium, indicating that during the process of homogenization the ability of the corneal epithelium to take up oxygen decreased notably. This same loss in oxygen uptake following homogenization was reported [18] to be present in many, though not all, of the tissues examined. It can be attributed to the destruction of certain cellular constituents and to the disorganization of the spatial arrangement of certain enzyme systems in the cells which apparently are necessary for optimum respiratory activity. Another factor might be a loss of coenzymes which occurs as a result of dilution. The fact that the addition of pyruvate and fumarate increases the oxygen uptake of the homogenized epithelium and maintains it at a higher rate for a considerable period of time indicates (1) that the removal of the cell membrane by homogenization probably allows these metabolites to come in contact with the intracellular enzyme systems and (2) that they are necessary for prolonged respiratory activity of the homogenized tissue. The inability of dextrose to increase the oxygen uptake of homogenized corneal epithelium, on the other hand, can be explained by the fact that the epithelium has a large carbohydrate content; thus, further addition of dextrose will only be in excess and consequently will not be utilized.

This experiment also demonstrates the superiority of the tissue slice method over the homogenization procedure.

IV. EFFECT OF METABOLITES ON THE OXYGEN UPTAKE OF THE CORNEA

In part III of this study it was demonstrated that the addition of pyruvate and fumarate increased the oxygen uptake of homogenized corneal epithelium. In order to ascertain whether this holds true also for the whole cornea, the following experiment was carried out.

TECHNIC

Oxygen uptake of fresh beef corneas was measured in Krebs's [13] medium IIa, as described in part II of this report. Pyruvate, fumarate and dextrose were added in final concentrations of 10, 25 and 100, per 100 cc., respectively.

RESULTS AND COMMENT

Table 6 shows that the addition of pyruvate, fumarate and dextrose did not affect the oxygen uptake of the excised beef cornea. This observation further emphasizes the peculiar metabolic behavior of the cornea, since in most tissues the respiratory activity is greatly increased by the addition of these metabolites. Of course, it is probable that these substrates do not penetrate into the intact cornea. Thus, one can

assume that if the obstructing barrier, i. e., the epithelial cell membrane, were removed, these metabolites would exert their effect on the respiratory activity of the cornea. This assumption was partially substantiated by the results of part III of this investigation, in which it was demonstrated that pyruvate and fumarate increased the oxygen utilization of the homogenized corneal epithelium.

TABLE 6.—*Oxygen Uptake of Bovine Corneas, in QO_2 Units,* Following the Addition of Pyruvate, Fumarate and Dextrose in Final Concentrations of 10, 25 and 100 Mg. per 100 Cc., Respectively*

Experiment No.	Control	Pyruvate, 10 Mg./100 Cc.	Fumarate, 25 Mg./100 Cc.	Dextrose, 100 Mg./100 Cc.
1	—0.59	—0.51	—0.52	—0.66
2	—0.53	—0.61	—0.62	—0.56
3	—0.60	—0.39	—0.59	—0.51
Average	—0.58	—0.57	—0.59	—0.58

* Microliters of oxygen absorbed per milligram dry weight tissue per hour, each figure representing one cornea.

SUMMARY

Excised bovine, cat and rabbit corneas were shown to respire in air. The respiratory quotient of bovine corneas in air was 1.00.

The excised bovine cornea maintains a steady rate of respiratory activity in the Warburg flask regardless of the composition or p_H of the suspending medium, the gas phase being either 100 per cent oxygen or air.

Homogenization of the corneal epithelium greatly decreases its ability to take up oxygen. The addition of pyruvate and fumarate increases the oxygen uptake of the homogenized corneal epithelium.

The addition of pyruvate, fumarate and dextrose does not affect the rate of oxygen utilization of the excised beef cornea.

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EXAMINATION OF THE ORA SERRATA

Its Importance in Retinal Detachment

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IT HAS long been recognized that ophthalmoscopy of the extreme periphery of the fundus has great significance in evaluating detachments, but few accurate and complete funduscopic observations have been recorded. In the latter part of the nineteenth century, the anterior limits of the visible fundus were determined both in clinical and in laboratory studies. The conclusions, however, were somewhat contradictory. In 1948, further experiments were conducted along these lines at the Massachusetts Eye and Ear Infirmary, in Boston, using the direct and the indirect method of ophthalmoscopy and comparing the results.

The ora serrata, which forms a transition zone between the pars optica and the pars ciliaris retinae, is located 7 to 8 mm. back of the limbus.[1] The retina is firmly attached to the choroid in this region. The ora makes a well defined serrated line, composed of approximately 48 toothlike projections of retinal tissue, directed anteriorly. These projections are separated by broad, rounded bays of pars plana. Neighboring teeth and bays often vary in size.

When examined with the ophthalmoscope, the outline of the ora serrata is seen distinctly because of a color contrast between the thin, reddish pars plana and the peripheral portion of the retina, which is thicker and grayish. Moreover, the anterior border of the ora is clearly demarcated by a narrow, serrated, pigmented band in the pars plana.

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1. Salzmann, M.: The Anatomy and Histology of the Human Eyeball in the Normal State: Its Development and Senescence, Chicago, University of Chicago Press, 1912, p. 84-85.

The retina adjacent to the ora serrata is practically free from visible vessels and shows a variable amount of diffuse pigmentation. Along the bays of the ora serrata one often sees a row of reddish vacuoles caused by cystoid degeneration.

The ora serrata is located 1 mm. nearer the limbus on the nasal side; therefore the pars plana is 1 mm. wider on the temporal side. According to several authors, this additional temporal width of the pars plana is the result of postnatal growth.

The nasal portion of the ora serrata differs considerably in appearance from the temporal portion. Temporally, the toothlike projections are short and attenuated, not exceeding 0.5 to 1 mm. in length—they may even be absent. The bays are narrow, and the pigment band is pronounced. Nasally, the bays of the ora are broad, and the pigmented band is very narrow. The toothlike projections are wide at their base, taper anteriorly and may be 2 to 2.5 mm. long. Sometimes they are even longer and reach the valleys between the ciliary processes.

It is possible that the asymmetry of the ora serrata is partly responsible for the location of certain pathologic changes in the temporal quadrants. It is known that approximately 80 per cent of retinal dialyses in young persons occur in the lower temporal quadrant. Typical retrolental fibroplasia, which tends to affect the region of the ora serrata, at an early stage, is also observed more frequently on the temporal than on the nasal side. So far, however, we have been unable to establish a definite correlation between these pathologic changes and the anatomic differences between the nasal and the temporal periphery.

The ora serrata and its underlying choroid seem to be mobile, moving slightly forward in accommodation. It has never been proved that this physiologic displacement is a definite factor in the causation of detachment. On the other hand, we have seen part of the ora displaced backward at an early stage of certain pathologic conditions. In some cases of retinal dialysis, for instance, one of the bays of the ora is pulled backward before a dialysis can actually be detected. It is not exceptional in such cases to see a ciliary process also being pulled back, probably by the fibers which connect it with an adjacent projection of the ora.

Anterior to the serrated border is the pars plana, which appears as a reddish area, striated meridionally. The striae consist of minute pigment clumps. The posterior portion of the pars plana contains the pigment band which lines the ora serrata. The middle part is relatively unpigmented. Anteriorly the pars plana reaches the base of the ciliary processes and shows diffuse pigmentation.

The only firm attachment between the vitreous and the retina is in the region of the ora serrata and pars plana. This union between the vitreous, on the one hand, and the ora serrata and pars plana, on the

other, is so close that it has been called a "symphysis."[1a] When the vitreous is torn off the globe at the symphysis, coarse shreds of ciliary epithelium adhere to it, even in the normal eye. The vitreoretinal symphysis is limited posteriorly by the serrated edge of the ora and anteriorly by a line located in the least pigmented part of the pars plana, halfway between the ora and the posterior edge of the ciliary processes. This anterior limit is sometimes visible with the ophthalmoscope as a gray and faintly serrated line. In many cases of detached retina, the posterior limit of the symphysis is moved back, occasionally as far as the equator.

Very little is known about the nature of the vitreoretinal symphysis. However, it is known that fine fibers originate from the retinal epithelium on the teeth of the ora and on the edge of the rounded bays. Many of these fibers extend into the vitreous, but they are not visible with the ophthalmoscope. When the vitreous retracts, it pulls on the vitreoretinal symphysis. In its earliest stage, this retraction may cause a limited detachment of the teeth of the ora or a slight elevation of the retina along the bays.

Between 1875 and 1895, Donders,[1b] Groenouw,[2] Schoen,[3] Magnus[4] and Druault[5] conducted experiments to determine how far anteriorly the sclera can be transilluminated through the pupil. From a number of experiments and calculations, they concluded that in an emmetropic eye this point was at or near the ora serrata, 7 mm. back of the limbus (fig. 1 *A*). This anterior limit is determined chiefly by the depth of the anterior chamber. When the anterior chamber is deep, the limit is located farther from the limbus than when it is shallow. On the other hand, if the anterior chamber is extremely shallow, the limit is only 5 mm. from the limbus (fig. 1 *B*). Other, less important factors influencing its location are corneal diameter, pupillary size, scleral radius of curvature and curvature of the anterior surface of the lens. Curvature of the cornea has apparently no influence. These results help to explain why the limit

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1a. Redslob, E.: Anatomie du globe oculaire, in Bailliart, P.; Coutela, C.; Omfray, R.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 1, p. 369-594.

1b. Donders, F. C.: Die Grenzen des Gesichtsfeldes in Beziehung zu denen der Netzhaut, Arch. f. Ophth. **23** (pt. 2):255-280, 1877.

2. Groenouw, A.: Wo liegt die vordere Grenze des ophthalmoskopisch-sichtbaren Augenhintergrundes? Arch. f. Ophth. **35** (pt. 3):29-56, 1889.

3. Schoen, W.: Die Funktionskrankheiten der Ora serrata und des Ciliartheiles der Netzhaut, Arch. f. Augenh. **30**:128-178, 1895.

4. Magnus, H.: Über ophthalmoskopische Erscheinungen in der Peripherie des Augengrundes, Arch. f. Ophth. **35** (pt. 3):1-28, 1889.

5. Druault, A.: Note sur la situation des images rétiniennes formées par les rayons très obliques sur l'axe optique, Arch. d'opht. **18**:685-692, 1898.

of visibility of the fundus is 2 mm. closer to the limbus in high hyperopes than in emmetropes and 2 mm. farther back in high myopes.

In cases of aphakia the sclera may be transilluminated as far as 6 mm. from the limbus, or 1 mm. farther than in emmetropia (fig. 1 *C*). This expansion of the field of transillumination results mainly from two factors: First, when the crystalline lens is present, rays obliquely incident to the optical axis of the eye are refracted posteriorly; second, incident rays which are extremely oblique are lost through total reflection by the lens.

If a + 20.00 D. lens is placed at the proper distance from the eye, it creates a cone of illumination with its apex in the pupillary plane (fig. 2). This increases to its maximum the size of the illuminated area on the sclera. The sclera of an emmetropic eye can then be transilluminated through the pupil up to approximately 6.5 mm. from the

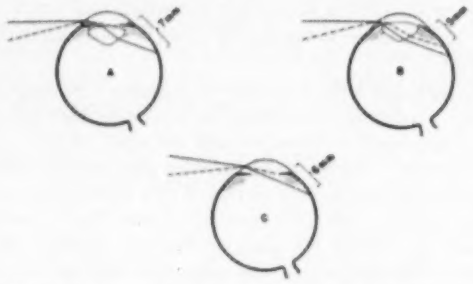

Fig. 1.—Diagrams showing how light travels through the pupil and illuminates the extreme periphery of the fundus.

A, emmetropic eye with an anterior chamber of normal depth. An extremely oblique ray (dotted line) does not reach the fundus of the eye because it is reflected by the anterior surface of the lens. The most peripheral area of the fundus that can be illuminated through the pupil is located about 7 mm. from the limbus. Oblique rays refracted by the lens are displaced toward the posterior pole of the globe.

B, emmetropic eye with a shallow anterior chamber. The oblique ray (dotted line), which was lost through reflection when the chamber was deep, is now refracted into the peripheral fundus, approximately 5 mm. from the limbus.

C, aphakic eye. The ocular media have an almost uniform refractive power. Contrary to what was observed in *A*, obliquely incident rays are neither reflected by the anterior surface of the lens nor displaced toward the posterior pole of the globe. Consequently, the limit is now about 6 mm. from the limbus.

limbus, instead of 7 mm. When one is examining the extreme periphery, it is of great importance to place the cone of illumination with its apex in the pupillary plane, because when viewed obliquely the pupil is reduced to a slit.

Ophthalmoscopic examination of the periphery of the fundus is more complicated than measurement of scleral transillumination through the

pupillary aperture.[5a] A series of experiments was performed using various methods of ophthalmoscopy, and the following conclusions were drawn:

1. If the media are cloudy, ophthalmoscopy requires greater intensity of illumination, with either the direct or the indirect method. With direct ophthalmoscopy, the image of the light source nearly coincides with the reflecting surface of the mirror or prism. The apex of the cone of illumination is located at some distance in front of the pupil, considerably diminishing the field of illumination in the fundus. This is particularly true when the periphery is examined, at which time the pupil is reduced to a slit. In the construction of direct ophthalmoscopes, other features result in less intense illumination than can be obtained with indirect ophthalmoscopes. The latter can be built with a light source which not only is very intense but also forms its image in the pupillary plane. This

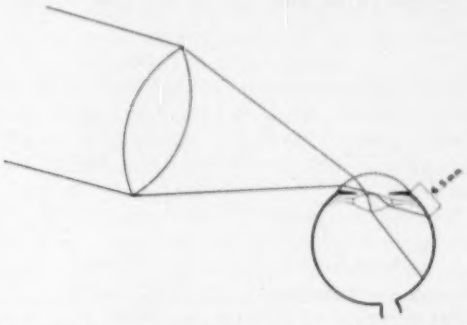

Fig. 2.—The use of a condenser, such as a sphere of + 20.00 D., increases the size of the illuminated area on the sclera. This permits transillumination up to 6.5 mm. from the limbus, instead of 7 mm.

is a decided advantage when one is examining the periphery of the fundus.

2. In direct ophthalmoscopy, one encounters another difficulty, and that is an increase of distortion as one progresses peripherally. This cannot be overcome by any combination of ordinary spherical and cylindric lenses. Distortion is so great that a peripheral band of retina several millimeters wide merely reflects a uniform reddish glow, with no fundus details. This reduces the limits of clear visibility of the ophthalmoscopic image. Only a small amount of distortion is encountered when an indirect ophthalmoscope with a + 20.00 D. condensing lens is used. The limits of the funduscopic view are then often determined by such

5a. Reimar, M.: Über die ophthalmoskopische Sichtbarkeit der Ora serrata und der Processus ciliares, Arch. f. Augenh. **41**:102-108, 1900.

anatomic barriers as the pupillary border and the outer limit of corneal transparency.

The extent of a clearly visible fundus was determined experimentally with direct and with indirect ophthalmoscopy, using the strongest light source available. Seven eyes were selected which had pathologic lesions in the anterior retina that could be used as landmarks. One investigator examined the fundus with the Schepens indirect ophthalmoscope [6]; the other used several types of direct ophthalmoscopes. The findings were recorded independently, in four meridians, and the results were compared. The distance between the landmarks and the limits of clear vision was estimated in disk diameters, according to Gonin's method. With indirect ophthalmoscopy the extent of clear visibility was 1 to 3 disk diameters greater than with the direct method of ophthalmoscopy.

In attempting to discover the cause of this difference, experiments were conducted on several enucleated human eyes. The cornea, iris and lens were removed, the cornea being replaced by a strong planoconvex lens. Optical continuity between the vitreous and the glass lens was maintained by means of a viscid

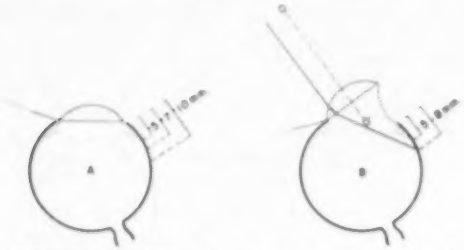

Fig. 3.—Diagram showing a human enucleated eye from which the cornea, iris and lens had been removed.

(*A*) The cornea was replaced by a planoconvex lens. With direct ophthalmoscopy, clear vision was obtained only up to about 10 mm. from the limbus. With indirect ophthalmoscopy and a condensing lens of + 10.00 D., the limit of clear vision was at about 7 mm. from the limbus. With a lens of + 20.00 D., the limit was at about 5 mm. from the limbus.

(*B*) The artificial cornea was tipped, and the periphery was examined along its optical axis *O O'*. Optical continuity between the glass lens and the eyeball was maintained by means of a methylcellulose solution (dotted line). The limit of clear vision with a direct ophthalmoscope was then located 8 mm. from the limbus, instead of 10 mm. With an indirect ophthalmoscope, the periphery was clearly seen up to 5 mm. from the limbus, where the ciliary body and the edge of the cornea were the limiting factors.

methylcellulose solution (fig. 3 *A*). The anterior limit of clear vision was marked on the overlying sclera, and the distance from the limbus was measured with a divider.

With direct ophthalmoscopy, the same difficulties were encountered as when one is examining an ordinary aphakic eye. Clear vision was

6. Schepens, C. L.: A New Ophthalmoscope Demonstration, Tr. Am. Acad. Ophth. **51**:298-301, 1947.

possible only up to 10 mm. from the limbus. With the indirect ophthalmoscope, using a + 10.00 D. condensing lens and a + 4.00 D. lens in front of the observer's eye, it was possible to see clearly about 3 mm. more anteriorly than with the direct method. When a + 20.00 D. condensing lens was used with a + 3.00 D. lens in front of the observer's eye, the fundus could be seen clearly 5 mm. more anteriorly.

Direct ophthalmoscopy magnifies the image of an emmetropic fundus approximately fifteen times. Indirect ophthalmoscopy with a + 10.00 D. condensing lens and a + 4.00 D. lens placed in front of the observer's eye magnifies the image about six times. If a + 20.00 D. condensing lens is used with a + 3.00 D. lens in front of the observer, the magnification is about 2.2 times. These experiments suggest the existence of a close relation between the amount of distortion and the magnification of the retinal image. Therefore, distortion is quite evident with direct ophthalmoscopy. With the indirect method, it is less noticeable if a + 10.00 D. condensing lens is used, and distortion is reduced to a minimum with a + 20.00 D. condensing lens.

With all the ophthalmoscopes used, the periphery of the retina was seen most clearly when examined along the optical axis of the artificial cornea. This was accomplished by tipping the artificial cornea (fig. 3 *B*). If, in clinical practice, the natural corneal surface could be replaced with an optical surface which could be easily tilted, magnification of the peripheral fundus would probably be obtained with less distortion.

In experienced hands, the best instrument for examination of the peripheral retina proved to be an indirect ophthalmoscope, with a strong light source and a + 20.00 D. condensing lens. Stereopsis, which emphasizes the level differences, is especially useful when one is examining the periphery of the retina. Parallactic displacement, used in monocular ophthalmoscopy, is helpful only between the disk and the equator; it is ineffective for the extreme periphery.

A few pertinent points on the pathology of the ora serrata should be stressed in connection with retinal detachment. Dufour and Gonin [7] were the first to recognize the significance of retinal breaks. Gonin [8] was also aware of the pathologic importance of shrinkage of the vitreous which often precedes the detachment of the retina. His observations revealed that retinal breaks often result from the pull of the retracting vitreous on an abnormal vitreoretinal adhesion. The vitreous never loses its normal attachment to the ora serrata and pars plana. Strong peripheral, retraction, however, may tear the retina in the region of the ora serrata, resulting in one or more dialyses.

7. Dufour, M., and Gonin, J.: Décollement rétinien, Encycl. franç. d'opht. **6**:975-1025, 1906.

8. Gonin, J.: Pathogénie et anatomie pathologique des décollements rétiniens, Bull. et mém. Soc. franç. d'opht. **33**:1-104, 1920.

Since ophthalmoscopic examination of the ora serrata is more easily performed after intracapsular cataract extraction, most of our clinical observations were made on aphakic eyes. The prognosis of retinal detachment with aphakia is poor, but the reasons for this are not fully known. One important factor may be the difficulty of localizing retinal breaks in such cases. When found, they are often peripheral, multiple and very minute. In many cases, some of the retinal breaks are not discovered before operation, and coagulation fails to cover them.

Most of the peripheral breaks in aphakic eyes appear to be of two types—small dialyses and retinal breaks related to meridional retinal folds. Both types are located at the ora serrata or in its vicinity. The first, which consists of small dialyses, develops gradually. The bays are pulled toward the disk and become deeper, causing the toothlike projections of the ora to elongate. The ciliary epithelium stretches, and finally dialyses form in the ora. The red choroid appears, bordered by the gray edge of the detached bays of the ora. One or more dialyses form in this way, each one occupying a single bay of the ora. Later, as the teeth themselves are torn from their attachments, several small dialyses may coalesce. If treatment is to be successful, detection of these small dialyses is imperative. In some cases the enlarged or displaced bays are dotted with clumps of pigment. They probably result from newly formed adhesions to the choroid, which have thus effected a spontaneous cure.

The small, and often multiple, dialyses observed in cases of detachment with aphakia seem to have no connection with the large solitary dialysis of the ora serrata observed in the lower temporal quadrant in some young adults. In aphakic eyes dialyses are generally found in the upper half of the fundus.

The case of Mrs. E. D., aged 49, is a typical example of small dialyses. In 1945 she had immature cataracts in both eyes, the one in the right eye being more advanced. In 1946 a detachment of the retina developed in her right eye and was operated on, with success. A few months later an uncomplicated intracapsular cataract extraction was performed, with a good visual result. Six months later she was referred to one of us for a relapse of her detachment; at that time a second operation was performed, with success. Eighteen months after the cataract extraction she had a second relapse of the detachment (fig. 4). The scar of the two previous operations covered the whole periphery except in the upper nasal quadrant. It showed good pigmentation, but a detachment was still present over the nasal half of the fundus. Besides retinal breaks at 3, 4 and 4:30 o'clock, there were two small dialyses between 1 and 3 o'clock. A third operation resulted in the reattachment of the retina, with a visual acuity of 20/70.

The second type of retinal break is associated with small retinal folds directed meridionally (fig. 5). These folds usually originate 1 to 3 disk diameters posterior to the ora and occasionally in the ora itself. They

extend anteriorly over the toothlike projections alone, and practically never over the bays of the ora serrata. Their anterior insertion is difficult to distinguish. Sometimes they appear stout, and pigmentary migration is seen about their posterior retinal attachment. This reaction probably results from their pull on the retina and is a form of spontaneous cure. In other cases they give rise to a minute retinal break,

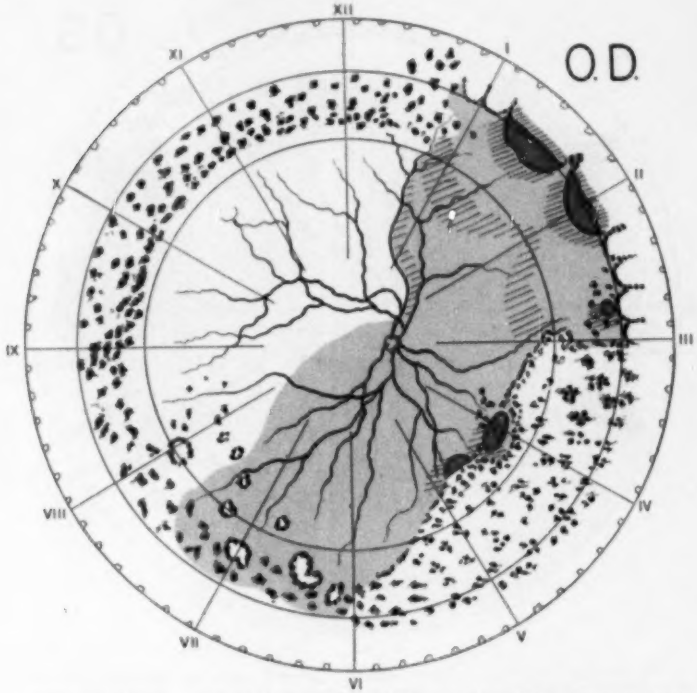

Fig. 4.—Diagram of the fundus of a right eye with aphakia (Mrs. E. D.). The inner circle of the diagram corresponds to the equator, the middle circle to the ora serrata and the outer circle to the posterior edge of the ciliary processes. The gray area represents detached retina; the shaded parts correspond to retinal folds. The pigmentation at the periphery is the result of previous operations. Small dialyses were present at 1:30 and 2 o'clock. Retinal breaks were detected at 3, 4 and 4:30 o'clock.

which occurs at, or slightly beyond, their posterior extremity. The nature of these folds will probably remain obscure until a correlation is made between ophthalmoscopic appearance and pathologic structure.

In 1908, Leber[9] fully described a cellular proliferation which crept over the retinal surface in old cases of retinal detachment, bridging retinal folds and often making them star shaped. He expressed the belief that the cells originated from the ciliary epithelium and that their proliferation was the primary cause of retinal detachment. Cellular

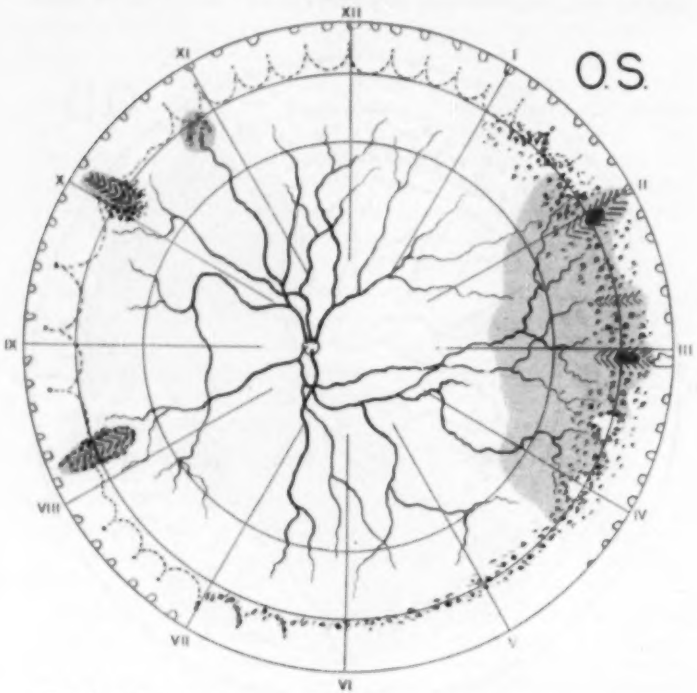

Fig. 5.—Left fundus of a man aged 67. Several years ago an uncomplicated intracapsular cataract extraction was performed on both eyes. In 1948 the right eye showed a total retinal detachment of long standing. In the left eye there was an early temporal detachment, detected by routine perimetry, which extended from 2 to 4 o'clock. The region of the ora serrata, on the temporal side, was excessively pigmented. At 8 and 10 o'clock were meridional folds, which were pigmented around their posterior edge. Other meridional folds, at 2 and 3 o'clock, showed a retinal break. At 3 o'clock a ciliary process was pulled backward by the fold. There was a smaller meridional fold at 2:30 o'clock. At 11 o'clock a small detachment without break was present. Treatment of the retinal breaks has resulted in reattachment of the retina.

9. Leber, T.: Über die Entstehung der Netzhautablösung. Ber. ü. d. Versamml. d. ophth. Gesellsch. Heidelberg **35**:120-134, 1908.

proliferation has also been reported over the surface of the retracted vitreous, sheathing its remaining adhesions to the retina. It is possible that glial proliferation originating in the retina may cause a similar ophthalmoscopic appearance. Gonin disagreed with Leber's interpretation and stated that cellular proliferation was a secondary change occurring at a late stage and immobilizing the detached retina and vitreous. There is no doubt that cellular proliferation in the vitreous is

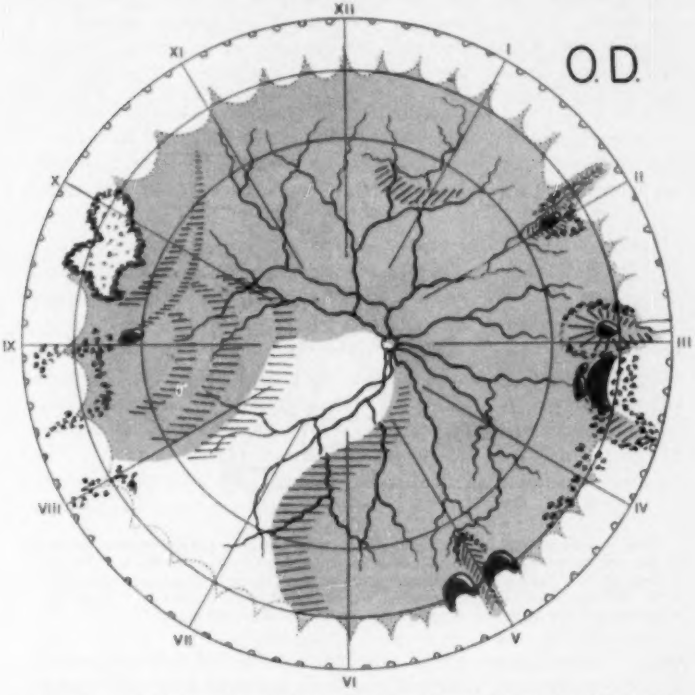

Fig. 6.—Association of small dialyses and meridional folds in the right fundus of a patient without aphakia. There was no myopia and no history of trauma. Additional retinal breaks were noted at 9, 2 and 3 o'clock. There was a scar of chorioretinitis between 9 and 10 o'clock.

more frequent and more pronounced in old detachments than in fresh ones. Therefore, it is likely that it often occurs as a secondary change. A primary alteration may be the retraction of the vitreous body. At the present stage of knowledge, we accept the hypothesis that meridional folds of the retina in the region of the ora serrata result primarily from

shrinkage of the vitreous. They are sometimes observed at a very early stage of detachment (fig. 5). We have also detected them before a clinical detachment was visible (fig. 7). It is not known whether these meridional folds are coated with glial cells, epithelial cells or connective tissue cells.

Other signs of peripheral retraction of vitreous can be observed in well established detachments with aphakia. One of its most typical manifestations is the appearance of a partial or complete circular fold in the retina. This is found near the equator and running parallel to it. In early cases it may affect only one quadrant, but it generally increases and becomes circular, involving the entire periphery. It is often steep on the side toward the disk and is partly covered by vitreous haze on

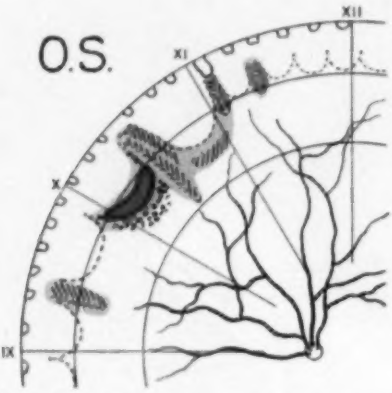

Fig. 7.—Meridional folds without clinical detachment in the upper nasal quadrant of the left fundus of the patient whose right fundus is shown in fig. 6. The small dialysis at 10 o'clock showed pigmentation on its edge, thus effecting a spontaneous cure. At 11 o'clock, a ciliary process was pulled strongly backward. In all other respects, this eye appeared normal. No operation was performed.

the side toward the ora serrata. Peripheral to the fold dialyses may form. We believe that a circular fold marks the posterior limit of the vitreoretinal symphysis, in a pathologic location. In advanced cases, the circular fold is prominent, and the dialyses it produces may coalesce and affect one half, three quarters or the whole of the circumference of the ora. When the retina is not torn at the ora, it appears stretched and very thin. We have noticed that heavy diathermy in the region of a circular fold induces even greater retraction of the vitreous. It is noted that circular folds also exist in phakic eyes.

As seen in figure 6, small multiple dialyses and meridional folds, with or without a retinal break near their posterior extremity, were often

observed in the same eye. This type of pathologic change was seen mostly in detachments with aphakia; however, in a few phakic patients we noticed identical changes.

Figures 6 and 7 represent the schematic drawings of the fundi of a phakic subject. The patient, a man aged 38, was emmetropic and showed no lenticular opacities in either eye. He had a spontaneous detachment in the right eye (fig. 6), which was fairly flat and spared only the lower temporal quadrant. There was a small dialysis at 3 o'clock and two more at 5 o'clock; meridional folds were discovered at 2, 3, 3:30 and 5 o'clock. The fold at 5 o'clock showed pigmentation around its posterior extremity; those at 2 and 3 o'clock had a small round hole near their posterior extremity. A ciliary process was clearly seen at 3 o'clock, being pulled backward by the meridional fold. Operation resulted in complete failure. The left eye appeared unaffected and showed no field defect. The fundus was normal except for the extreme periphery of the upper nasal quadrant (fig. 7).

From the observation of several similar cases, we concluded that the changes in the ora, so frequently observed in detachments associated with aphakia, also exist in phakic patients. In the case of Mrs. E. D. (fig. 4), a detachment was diagnosed and operation was performed before the cataract extraction. It is felt that in many other cases of detachment associated with aphakia the detachment is probably present before the lens is extracted. It seems, therefore, that the cataract extraction is not an important cause of this type of detachment, but acts only as a precipitating factor. It is more logical to assume that there is an undetermined primary cause for the detachment and that, for some reason, a cataract also tends to develop in these eyes.

SUMMARY

Under the ophthalmoscope, the ora serrata appears as a serrated, pigmented line. The nasal serrations differ in appearance from the temporal ones. An early pathologic change is the backward displacement of one of the bays of the ora. This may be the earliest form of retinal dialysis. The pars plana is 1 mm. broader on the temporal side. Sometimes it shows a faint gray line parallel to the ora serrata, which is probably the anterior limit of the vitreoretinal symphysis.

Experiments performed on patients and on enucleated eyes proved that for the examination of the extreme periphery of the fundus indirect ophthalmoscopy is definitely superior to the direct method. The main obstacle with use of a direct ophthalmoscope is the greater magnification, which blurs the image of the periphery. Stereoscopic indirect ophthalmoscopy, with a strong light source and a +20.00 D. condensing lens, seems to be the most effective method.

In cases of detachment associated with aphakia, two types of retinal breaks have often been observed near the ora serrata: small dialyses, and retinal breaks related to meridional retinal folds. The cause of the meridional folds is uncertain.

The changes described have also been observed in some phakic patients with detachment. It seems, therefore, that uncomplicated extraction of the lens is not an important cause of the type of detachment under consideration.

OCULAR HYPERTENSION INDUCED BY AIR IN THE ANTERIOR CHAMBER

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THE PURPOSE of this paper is to report observations showing that air injected under normal pressure into the anterior chamber of man and certain experimental animals can induce rapid increases in ocular tension, which may reach very high levels. This action indicates that the injection of air into the anterior chamber is not an innocuous procedure which can be carried out indiscriminately. In certain situations its use is probably contraindicated, the injection of saline solution being preferable. The elevation in tension is caused by obstruction to the flow of aqueous from the posterior to the anterior chamber as a result of a valvelike action between the posterior surface of the air bubble and the anterior surface of the iris. Aqueous therefore is retained behind the iris and, being unable to escape from the eye, causes an increase in ocular tension. As aqueous accumulates in the posterior chamber, the root of the iris is pushed forward, presenting the appearance of an iris bombé, and the ocular tension begins to rise (fig. 1). As more aqueous is formed and the tension increases, the periphery of the iris is forced anteriorly and a fold of iris tissue forms and insinuates itself between the corneoscleral wall and the air bubble. This fold frequently extends forward onto clear cornea for several millimeters. The pupillary border of the iris is simultaneously pulled peripherally and, in experimental animals, is eventually displaced around the edge of the air bubble until the valvelike mechanism is lost. The tension then falls rapidly because the aqueous is permitted to enter the anterior chamber and escape from the eye through normal channels at the angle of the anterior chamber.

The increasing use of air injected into the anterior chamber after surgical procedures makes imperative the recognition of any complications which might follow. Intraocular injection of air has been used for

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several purposes. Rohmer,[1] in 1912; Jeandelize and Baudot,[2] in 1926, and others injected air into the vitreous for the treatment of retinal detachment. Koster,[3] in 1902, was apparently the first to inject air into the anterior chamber for the treatment of nodular iritis, probably tuberculous. Selinger [4] and others have suggested its introduction into the anterior chamber after cataract extraction. MacMillan [5] placed air in the anterior chamber after corneoscleral trephinations. Injection of air has also been used in the treatment of delayed reformation of the anterior chamber following cataract extraction. Barkan [6] and others advocated the use of air in the anterior chamber following cyclodialysis, both to keep the cleft open and to act as a hemostatic agent. Barkan,[7]

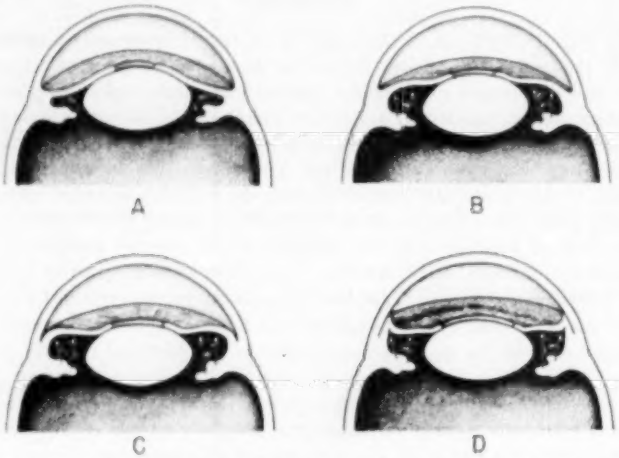

Fig. 1.—*A*, anterior chamber filled with air; *B* and *C*, iris pushing forward; *D*, periphery of iris pushing forward along the corneoscleral wall.

1. Rohmer: Effets des injections d'air stérilizé dans le vitré contre le décollement de la rétine, Arch. d'opht. **32**:257-274, 1912.

2. Jeandelize, P., and Baudot, R.: À propos du traitement chirurgical du décollement spontané de la rétine, Arch. d'opht. **43**:413-414 (July) 1926.

3. Koster, W. O.: Klin. Monatsbl. f. Augenh. **40**:340, 1902.

4. Selinger, E.: Injection of Air into the Anterior Chamber After Cataract Extraction, Am. J. Ophth. **20**:827-828 (Aug.) 1937.

5. MacMillan, J.: Injection of Air as Factor in Maintaining Filtration After Corneoscleral Trephining in Glaucoma, Arch. Ophth. **22**:968-973 (Dec.) 1939.

6. Barkan, O.: Cyclodialysis, Multiple or Single, with Air Injection: An Operative Technique for Chronic Glaucoma, Am. J. Ophth. **30**:1063-1073 (Sept.) 1947.

7. Barkan, O.: Goniotomy: Preliminary Deepening of the Anterior Chamber with Air or Saline Solution, Am. J. Ophth. **28**:1133-1134 (Oct.) 1945.

in 1945, first suggested filling the anterior chamber with air to visualize the angle of the anterior chamber when one is doing a goniotomy. Maumenee,[8] more recently, has advocated a similar technic. Scheie [9] has employed air in the anterior chamber after goniotomy to prevent synechias along the line of the incision. The rationale for the use of air after operation has been the prevention of undesirable adhesions which might occur if the anterior chamber were permitted to remain empty. Hughes and Cole [10] have recently reviewed the literature on the subject.

Little mention of complications following injection of air is found in the literature. Von Sallmann,[11] when studying the effect on the composition of aqueous humor of injection of air into the anterior chamber, stated that the intraocular pressure occasionally becomes elevated after the injection of air. Barkan,[6] while advocating the use of air after cyclodialysis, noted in passing that a progressive rise in intraocular pressure might occur, probably the result of air blocking the free circulation of aqueous. He stated that when this did occur there was a sufficient quantity of air under pressure to produce seclusion of the pupil, a condition which in some cases was combined with obstruction of the angle. He warned that, in view of this danger, only a limited quantity of air should be allowed to remain in the anterior chamber after operation to maintain the cleft opening. He carried the observation no further. O'Brien,[12] in discussing a paper by Hughes and Cole,[10] mentioned that if air passes through the pupil to insert itself back of the iris glaucoma can result.

Our attention was first called to elevation in ocular tension following the injection of air into the anterior chamber when we observed an attack of acute congestive glaucoma which followed shortly after aspiration of the anterior chamber with replacement of aqueous by air. The patient, a white woman aged 65, had been under treatment for chronic simple glaucoma of the wide angle type. Previous gonioscopic examination had revealed open angles of the anterior chamber. At 3:30 p. m. on Feb. 16, 1949, aqueous was aspirated from the anterior chamber of her left eye and the chamber filled with air injected under very slight pressure. About one and one-half hours later she began to complain of severe pain in the eye. Examination revealed conjunctival injection and edema, accompanied with bedewing of the corneal epithelium. The

8. Maumenee, A. E.: Personal communication to the authors.

9. Scheie, H. G.: Goniotomy in the Treatment of Congenital Glaucoma, Arch. Ophth. **42**:266-282 (Sept.) 1949.

10. Hughes, W. L., and Cole, J. G.: Technical Uses of Air in Ophthalmology, Tr. Am. Ophth. Soc. **43**:115-135, 1945; Arch. Ophth. **35**:525-540 (May) 1946.

11. von Sallmann, L.: Air Insufflation into the Anterior Chamber, Nat. M. J. China **17**:6-17 (Feb.) 1931.

12. O'Brien, C. S., in discussion on Hughes and Cole.[10]

anterior chamber was very shallow, and the iris presented somewhat the appearance of iris bombé. The iris was in contact with the cornea peripherally, where it bulged forward conspicuously; but the pupillary border of the iris was in contact with the lens. The anterior chamber, though shallower, remained filled with air. The tension of the eye was 70 mm. of mercury (Schiøtz).

We immediately suspected glaucoma due to iris block, caused possibly by partial loss of the air from the anterior chamber, which had allowed the cornea and the iris to come into contact, obstructing the angle. We therefore attempted to insert more air into the chamber in order to push the iris backward and reopen the angle. On insertion of the needle, the remaining air, as well as some aqueous, escaped. The eye immediately became soft, but, hoping to keep the angle open, we again filled the entire chamber with air sufficient in amount to deepen the chamber considerably. As a precautionary measure, to hold the angle open, pilocarpine nitrate and physostigmine salicylate were dropped into the conjunctival cul-de-sac. Relief was only temporary, however, for in two hours the pain and elevation of tension recurred, accompanied with nausea and vomiting. Examination of the eye revealed the same appearance as that noted after the first injection of air. The iris was again bulging forward and was in contact with the cornea peripherally. Again, air remained in the anterior chamber. At 8:00 on the following morning, because the symptoms and elevation of ocular tension had continued unchanged, the air was once more completely removed from the anterior chamber; but this time the chamber was allowed to remain empty. The ocular tension, however, promptly rose again; and finally, at 3:00 p. m., 24 hours after the original procedure, an iridencleisis was done. This operation has successfully controlled the tension up to the time of this report.

The reason for the rise in tension was obscure. Several possibilities presented themselves. The first was closure of the angle through adhesion of the iris to the trabecular region of the angle, such as might have occurred if the air had escaped and the chamber had emptied. This did not seem feasible, however, because air remained in the chamber and subsequent reinjection of sufficient air to deepen the chamber did not prevent a second rise in tension. The second possible explanation was the precipitation of a neurovascular crisis as a result of the trauma of paracentesis, with ensuing rapid rise in tension. The third possibility was obstruction of the normal flow of aqueous from the posterior to the anterior chamber, resulting from a valvelike action exerted by the posterior surface of the air bubble and the anterior surface of the iris. This mechanism has been described by Friedenwald and Pierce[13] as

13. Friedenwald, J. S., and Pierce, H. F.: The Circulation of the Aqueous: Rate of Flow, Arch. Ophth. **7**:538-557 (April) 1932.

following anterior dislocation of the lens. Such an explanation could, of course, account for the pushing forward of the iris, to resemble an iris bombé, and the subsequent contact of the iris with the corneoscleral wall as aqueous accumulates behind the iris. Fibrinous adhesions might then form between the iris and the trabecular region, as in acute congestive glaucoma, thus perpetuating the increase in ocular tension, even after removal of the air from the anterior chamber. This probably occurred in the case just described, in which an iridencleisis had to be done to control the tension. The following experiments were undertaken to study the effect of injection of air into the anterior chamber on ocular tension.

EXPERIMENTAL TECHNIC

Experiments were outlined to determine the effect of the injection of air into the anterior chamber on the ocular tension in animals and, if possible, to make further observations in man. Rabbits, dogs and cats were used for the animal experimentation. The experiments on dogs and cats were done with the animals under intravenous pentobarbital (nembutal®) anesthesia. Those with rabbits were done with local anesthesia, instillations of tetracaine sufficing. The rabbits were immobilized in a rabbit box. Tensions were recorded with a Schiøtz tonometer or with a mercury manometer. A sharp no. 27 needle was inserted at the limbus very obliquely, traversing several millimeters of corneal tissue before entering the anterior chamber, to insure a self-sealing wound which could retain the air. Aqueous was aspirated and air injected with the same needle in place. The eyes were observed at frequent intervals for any changes which might occur. The intraocular tension was recorded at the time of each inspection.

EXPERIMENTAL RESULTS

A. ANIMAL EXPERIMENTS

1. *Effect of Injection of Air into the Anterior Chamber on the Intraocular Tension of Normal Animal Eyes.*—Pilot experiments were made, consisting of aspiration of the anterior chamber of normal rabbit, dog and cat eyes, followed by the injection of air. In all instances the air was injected until the ocular tension measured no less than 10 mm., or more than 25 mm., of mercury, as determined with the Schiøtz tonometer. Observations showed that the ocular tension in nearly all dog and rabbit eyes began to rise very shortly, reaching a maximum within 30 to 60 minutes, when levels of 60 mm. of mercury or more were recorded. Cat eyes were less satisfactory to work with because of the large volume of the anterior chamber. As a result, future experiments were limited to the eyes of rabbits and dogs. In all animals the iris was pushed forward and the anterior chamber became shallow as the ocular tension increased (fig. 1). Immediately after the injection of air the chamber was usually deeper than normal and the angle visible in its entirety. As the ocular tension began to rise, the periphery of the iris could be seen to bulge forward and the air bubble became smaller, being compressed toward the central zone of the anterior chamber. The pupillary portion

of the iris remained in contact with the lens, where it was held by the air bubble. With increasing levels of ocular tension, the periphery of the iris continued to bulge forward, resembling an iris bombé. The face of the iris soon came into contact with the corneoscleral wall, and in most instances this contact extended upward well onto clear cornea before the end of the experiment.

As the iris was pushed forward, the pupillary border was displaced, and aqueous eventually escaped around the edge of the bubble of air, thus allowing the ocular tension to return to normal. This usually required from one and one-half to three hours with the animal in the upright position. With the animal in this position, the air tended to rise to the upper portion of the anterior chamber, so that as aqueous was formed it settled in the lower portion of the posterior chamber, pushing the lower portion of the iris conspicuously forward. This led to early displacement of the lower pupillary border around the air bubble, with rapid lowering of tension. In our pilot experiments we also found that if insufficient air was injected into the anterior chamber an elevation in tension did not occur.

2. *Effect of Injection of Air into the Anterior Chamber into Rabbit and Dog Eyes with Pupils Dilated by 10 Per Cent Phenylephrine (Neo-Synephrine®) Hydrochloride Solution.*—If the rise in ocular tension results from a valvelike action between the air bubble and the iris which obstructed the forward flow of aqueous, wide pupillary dilation should prevent such a rise. We therefore widely dilated the pupils of 10 rabbit eyes and a like number of dog eyes by two instillations of 10 per cent phenylephrine hydrochloride solution at five minute intervals. Aqueous was then aspirated from the anterior chamber and replaced with air, as previously described. In no instance in which the pupil was dilated more than 7 mm. did a subsequent rise in ocular tension occur. If the pupil was 6 mm. in diameter or less, the tension rose to high levels and persisted for the same length of time as in the previous experiments.

3. *Effects of Injection of Air into the Anterior Chamber of Eyes with Iridectomy.*—Experiments were carried out to determine the effect of peripheral and complete iridectomy on the elevation in tension following injection of air into the anterior chamber. In three eyes in which peripheral iridectomies had been performed, the ocular tension rose only insignificantly after injection of air, whereas, of the other three eyes, an elevation of 40 mm. of mercury occurred in one and of 47 mm. in the other two. The rise, however, went no further, a situation which we are unable to explain unless a certain amount of aqueous flowed into the anterior chamber through the iridectomy opening. Complete iridectomy was performed on several rabbit eyes and the same experiment carried out. No rise in tension in any of the eyes occurred. These

experiments were considered further evidence of the valvelike action between the iris and the air bubble.

4. *Duration of Elevated Ocular Tension in Dog and Rabbit Eyes Resulting from Injection of Air into the Anterior Chamber.*—The elevation in ocular tension produced in the previous experiment by injection of air into the anterior chamber subsided spontaneously in one and one-half to three hours as a result of displacement of the pupillary border around the air bubble, which permitted aqueous to enter the anterior chamber and presumably to escape through the angle. This always occurred through the lower pupillary border because with the animal in an upright position the air bubble rose toward the upper portion of the eye and the aqueous gravitated downward, pushing the lower portion of the iris forward. An apparatus therefore was devised

Duration of Ocular Hypertension Resulting from Injection of Air into Anterior Chamber with Lens-Iris Diaphragm Maintained in Horizontal Position

Animal	Tension Immediately Following Air Injection	Maximum Subsequent Tension, Mm. Hg (Schiøtz)	Duration of Rise in Tension, Hr.
Rabbit 3, O.D.	10	60 +	8
Rabbit 4, O.D.	20	60 +	8½
Rabbit 5, O.S.	10	60 +	8
Rabbit 6, O.D.	10	60 +	6 +
Rabbit 7, O.D.	12	60 +	6 +
Rabbit 8, O.D.	10	60 +	7 +
Rabbit 9, O.S.	20	60 +	5½
Dog 1	10	60 +	11
Cat 1	10	60 +	3

which held the head of the rabbit in such a position that the lens-iris diaphragm was horizontal. The air in the anterior chamber then remained centrally placed, exerting a uniform pressure around the entire pupillary border of the iris. In these experiments, the elevation of ocular tension occurred as before, but it persisted longer (table). The entire periphery of the iris became elevated and pushed forward in contact with the cornea, and the ocular tension remained at a very high level for five and one-half to seven hours before it fell, in contrast to one and one-half to two hours when the head was upright.

For greater accuracy, experiments were carried out in which tensions were recorded with a mercury manometer. Experiments were carried out on four dog eyes to determine the rate of increase in tension which followed the injection of air. The tension rose in an almost constant manner in these animals during the first hour (fig. 2), after which it became stabilized and remained fairly constant for two to three hours. The animals were not followed longer than this.

An attempt was made to determine how long the elevation in ocular tension could be maintained. For this purpose, dogs were chosen, because of their greater stability under anesthesia. The animals were anesthetized with pentobarbital sodium, intravenously administered, and supplemented at intervals in order to maintain an adequate level of anesthesia. The intraocular pressure was measured with a mercury manometer. The lens-iris diaphragm was maintained in the horizontal position to keep the bubble of air over the central portion of the iris and pupil. Three dogs were used. In all these animals the tension rose in the usual manner after injection of air and remained at a constant level throughout the experiment. The pressure was maintained for 22 hours in the first of these dogs, for 19 hours in the second and for

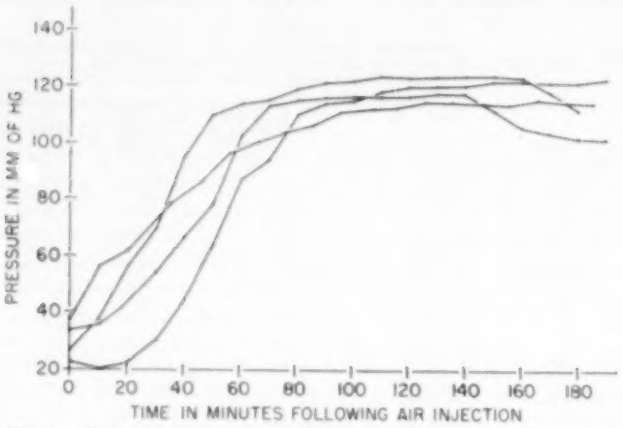

Fig. 2.—Graph showing rise in intraocular pressure in four dog eyes after injection of air into the anterior chamber.

14 hours in the third. In each case the intraocular pressure was still elevated when the experiment was concluded, on the death of the animal. At this time the iris was still in contact with the cornea over its entire circumference, and no aqueous was present in the anterior chamber.

B. CLINICAL EXPERIMENTS

Patient 1.—Mrs. E. B., a white woman aged 38, was admitted to the ophthalmology service, Hospital of the University of Pennsylvania, on July 19, 1949, for enucleation of her right eye because of what appeared to be a solid retinal detachment in the temporal portion of the right eye. She had noticed blurred vision for three weeks.

Ophthalmologic examination revealed no abnormality except the retinal detachment, solid in appearance, in her right eye. The anterior segment was normal. The angle of the anterior chamber was open. The ocular tension was normal.

Experimental Data.—The patient gave permission for the clinical experiment to be described. She was taken to the operating room, where a retrobulbar injection of 1 cc. of 4 per cent procaine hydrochloride was made into the muscle cone of the right eye. The ocular tension following this injection was 22 mm. of mercury (Schiötz). Aqueous was then aspirated from the anterior chamber, and air was injected at 4:30 p. m., until the ocular tension in the treated eye was 17 mm. of mercury and the chamber was full of air (fig. 3). The chamber appeared to be deeper than normal. The angle was easily seen as a result of the air in the anterior chamber. Observations on the anterior segment were made at 15 minute intervals with the low magnification of a slit lamp microscope and the Barkan hand light for illumination. The ocular tension was determined at half-hour intervals. At 5:30 p. m., one hour after the chamber had been filled with air, the tension was still 17 mm. of mercury, and the canal of Schlemm was still full of blood. The anterior chamber remained deep. By 6:00 p. m.,

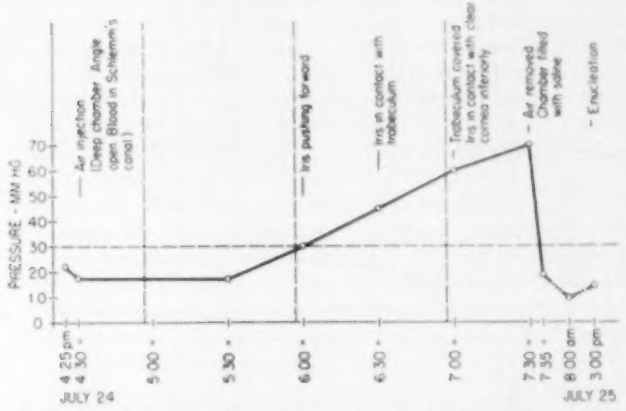

Fig. 3.—Graph showing rise in intraocular tension following injection of air into the anterior chamber in patient 1.

however, the tension had reached 30 mm. of mercury. Examination of the eye revealed definite shallowing of the anterior chamber, although the pupillary border of the iris was in firm contact with the lens. The periphery of the iris had begun to bulge forward. The canal of Schlemm no longer contained blood. By 6:30 p. m. the tension had climbed to 45 mm. of mercury. The iris could then be seen to be pushed farther forward, and peripherally it was in contact with the posterior trabecular region. By 7:00 p. m. the tension had reached 60 mm. of mercury. The iris had been pushed farther forward over the trabecular area and extended onto clear cornea from 4:30 to 10:30 o'clock. At 7:30 p. m., the ocular tension was 70 mm. of mercury, and the iris was in contact with the cornea over a greater portion of its circumference. At this point the air was aspirated from the anterior chamber, and, although the tension fell, it was found that the periphery of the iris did not drop away from the cornea, probably owing to peripheral synechia. Since we feared a secondary rise in tension, sufficient saline solution was injected to deepen the anterior chamber and open the angle. During the following 12

hours the tension remained low and was subnormal, just prior to enucleation, at 3:00 p. m.

PATIENT 2.—H. S., a white woman aged 31, was admitted to the ophthalmology service, Hospital of the University of Pennsylvania, for enucleation of her left eye because of metastatic carcinoma of the choroid, which had followed amputation of her left breast in 1947 for proved carcinoma. Numerous metastatic lesions were found throughout each lung field.

Examination of her eyes revealed a solid detachment along the inferior temporal vessels of her left eye, compatible with the diagnosis of metastatic neoplasm. No other abnormality was found. The anterior segment of each eye was normal. Gonioscopic examination revealed the chamber angles to be open.

Ocular tension was 20 mm. of mercury in the right eye and 17 mm. of mercury in the left eye (Schiøtz).

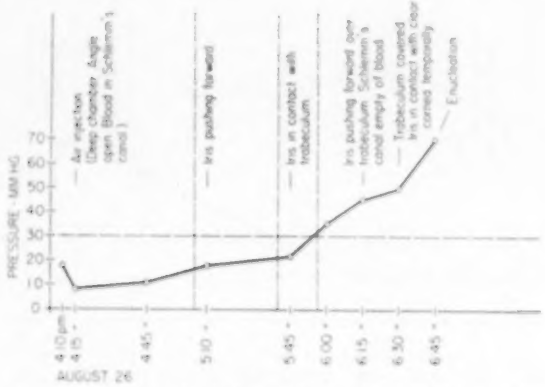

Fig. 4.—Graph showing rise in intraocular tension following injection of air into the anterior chamber in patient 2.

Experimental Data.—The nature of the experiment to be undertaken was explained to the patient, who gave her consent for the procedure. She was taken to the operating room, where a retrobulbar injection of 4 per cent procaine hydrochloride was made into the muscle cone of the left eye at 4:00 p. m. on Aug. 26, 1949. The tension of the eye at 4:10 p. m. was 19 mm. of mercury (Schiøtz). The anterior chamber was emptied of aqueous and refilled with air, after which procedure the tension reading was only 8 mm. of mercury with a Schiøtz tonometer (fig. 4). Examination of the angle of the anterior chamber with a slit lamp microscope and Barkan light revealed the angle to be wide open and the anterior chamber deep. The canal of Schlemm was full of blood. This condition remained unchanged until 5:10 p. m., when the tension had risen to 19 mm. of mercury. The anterior chamber at this time was definitely shallower, and the periphery of the iris was bulging forward. The pupillary border of the iris remained in contact with the lens. The tension rose to 22 mm. by 5:45 p. m. and to 35 mm. of mercury by 6:00 p. m. At that time the iris had pushed forward

even farther and had begun to come in contact with the trabecular area temporally. The canal of Schlemm still contained blood. By 6:30 p. m. the tension had risen to 50 mm. of mercury (Schiøtz), and the iris had ascended over the trabecular area around most of its circumference, and even onto clear cornea temporally. By 6:45 p. m. the tension had risen to 70 mm. of mercury; and, because the patient was very uncomfortable, enucleation was performed.

COMMENT

The observations presented here seem to offer sufficient proof that pronounced elevations in ocular tension may result from the injection of air into the anterior chamber. The air need be injected only under very low pressures, in the range of 10 mm. of mercury or even less, to produce this phenomenon. The rise in tension is almost certainly due to obstruction of the flow of aqueous from the posterior to the anterior chamber as a result of a valvelike action between the posterior surface of the air and the anterior surface of the iris. Friedenwald attributed the glaucoma which follows dislocation of the lens into the anterior chamber to the same principle, a ball valve action between the lens and the iris. The fact that the rise in tension can be prevented if the pupil is widely dilated or an iridectomy is performed offers further support for the hypothesis that a ball valve effect is the cause.

The ocular tension begins to rise as soon as sufficient aqueous has been formed in the posterior chamber. With the accumulation of aqueous in the posterior chamber, the iris is pushed forward peripherally, the condition at first somewhat resembling iris bombé. As tension increases, the iris pushes forward peripherally, tending to fold on itself and become tucked forward between the corneoscleral wall and the lateral aspect of the air bubble, frequently extending 2 to 4 mm. onto clear cornea in experimental animals. As this occurs, the pupillary border is displaced laterally and eventually slips around the lateral portion of the air bubble, and the valvelike action is lost. The tension then rapidly returns to normal. This occurs much more rapidly when the lens-iris diaphragm is in a vertical position than when it is horizontal, in which position the air remains centrally placed and the aqueous accumulates uniformly around the posterior surface of the iris. When the diaphragm is vertical, the ocular tension usually remains elevated from one and one-half to two and one-half hours; when it is horizontal the duration is longer.

Experiments on human subjects to study the duration of the increased tension following injection of air could not be carried out, but in a case in which air was allowed to remain in the anterior chamber for 15 hours the ocular tension remained elevated even after evacuation of the air. This was probably due to peripheral anterior synechia, which bound the iris to the trabeculum, for the tension was subsequently controlled by an iridencleisis.

The fact that injection of air can precipitate acute increases of ocular tension seems of considerable clinical importance in view of the increasing use of air after operation. Certainly, one should be very hesitant in placing any but small amounts of air into a tightly sealed anterior chamber, such as that which follows a cyclodialysis, a paracentesis or a goniotomy. The present experiments suggest that if air is used the pupil should be dilated widely. The observations presented in this paper suggest that the injection of air into the anterior chamber is probably contraindicated after cyclodialysis, because any appreciable amount of air would obstruct the pupillary space, and aqueous accumulating in the posterior chamber tends to seal the cyclodialysis cleft by exerting pressure on the iris and ciliary body, forcing them against the corneoscleral wall. If air is used for hemostatic purposes, after cyclodialysis, probably all but a very small amount should be released once the bleeding is under control. In most situations in which it is desirable to avoid postoperative synechia, as after goniotomy, it is probably much more logical to use saline solution than air, for saline solution, although retained for a shorter time than air, seems adequate for this purpose.

The use of air in the anterior chamber may well be of future experimental usefulness in conducting studies on formation and flow of aqueous, particularly at various pressure levels. The posterior chamber can be separated from the anterior chamber by this technic, which might permit studies on aqueous as formed in the posterior chamber.

Elevations in ocular tension induced by the injection of air into the anterior chamber in many ways simulate attacks of acute congestive glaucoma. The tension rises rapidly and shows no tendency to regress until the obstructive element, in this case the ball valve effect between iris and air, has been relieved in some fashion. In man, the secondary element of peripheral anterior synechia, causing adhesion of the iris and trabeculum, with perpetuation of the glaucoma, even after the removal of air, was noted.

CULTIVATION OF CONJUNCTIVAL AND CORNEAL TISSUE ON THE CHORIOALLANTOIC MEMBRANE

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THE CULTIVATION of the viruses of inclusion conjunctivitis and trachoma in tissue culture, even of susceptible human conjunctival epithelium, has failed up to the present time. Unlike most other viruses, neither the virus of trachoma nor that of inclusion conjunctivitis has been cultivated with certainty on the developing chick embryo. The present study was undertaken in an attempt to transplant conjunctival and corneal tissue of the rabbit to the chorioallantoic membrane of the developing chick embryo and to determine whether or not the transplanted conjunctiva and cornea would support the growth of various viruses. It was hoped that the results might provide a key to the successful cultivation of the viruses of trachoma and inclusion conjunctivitis.

In 1912 Murphy [1] demonstrated the possibility of grafting malignant tumors on the chorioallantois of the chick embryo. The grafts grew until the eighteenth or nineteenth day of incubation. In 1938 Goodpasture and co-workers [2] reported the successful grafting of human and rabbit skin on the chorioallantois of chick embryo. Grafts were implanted on the membrane of 10 day old embryos and studied over a period of from eight to 10 days. These grafts of human skin were inoculated with vesicular material from the eruptions of varicella and herpes zoster and with material from nodules of molluscum contagiosum, with consistently negative results. The lack of success led Goodpasture and his co-workers [3]

From the Department of Ophthalmology, Istanbul University, Turkey. This work was done in the Proctor Laboratory for Research in Ophthalmology, University of California Medical School, San Francisco.

1. Murphy, J. B.: Transplantability of Tissues to the Embryo of Foreign Species: Its Bearing on Questions of Tissue Specificity and Tumor Immunity, J. Exper. Med. **17**:482-493, 1913.

2. Goodpasture, E. W.; Douglas, B., and Anderson, K.: A Study of Human Skin Grafted upon the Chorio-Allantois of Chick Embryos, J. Exper. Med. **68**:891-904, 1938.

3. Goodpasture, E. W., and Anderson, K.: Virus Infection of Human Fetal Membranes Grafted on the Chorio-Allantois of Chick Embryos, Am. J. Path. **18**:563-575, 1942.

(1942) to the use of human embryonic tissue for similar experiments. These experiments demonstrated successfully that the human amnion and chorion could be grafted on the chorioallantois of developing chick embryo and could be infected with the viruses of herpes simplex, variola and vaccinia. Goodpasture and Anderson [4] later (1944) successfully infected similar grafts with the viruses of herpes zoster, to which the tissue of the chick embryo itself appears to be insusceptible. Blank, Coriell, and Scott [5] also reported (1948) successful results with herpes zoster virus, and in their experiments typical inclusion bodies developed in the epithelial cells of the human skin which had been grafted onto the chorioallantois.

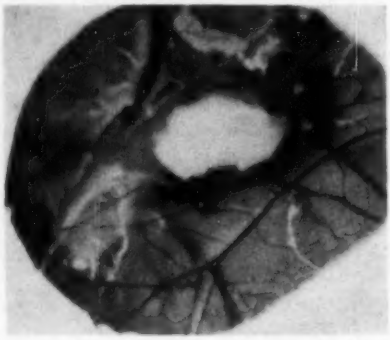

Fig. 1.—Rabbit conjunctiva grafted on the chorioallantois; duration of graft, three days.

MATERIALS AND METHODS

In order to obtain primary and serial transfer of conjunctival and corneal tissue onto the chorioallantoic membrane of the developing chick embryo, eggs of from nine to 11 days' prior incubation were selected. A circular area of the shell over the embryo was scored lightly with a drill, and a small slit was made with a stiff needle on the exposed shell membrane, care being taken not to puncture the underlying chorioallantoic membrane. A smaller hole was then made into the air sac and the air withdrawn. As a result, the embryo dropped away from the shell membrane, and a wide oval window was then made over the embryo by cutting the eggshell and shell membrane, thus exposing the chorioallantois.

For transplantation purposes, the bulbar conjunctiva was removed from the rabbit's eye to the extent of its full thickness. A graft measuring from 0.5 to 1.0

4. Goodpasture, E. W., and Anderson, K.: Infection of Human Skin Grafted on the Chorio-Allantois of Chick Embryos, with the Virus of Herpes Zoster, Am. J. Path. **20**:447-455, 1944.

5. Blank, H.; Coriell, L. L., and Scott, M.: Human Skin Grafted upon the Chorio-Allantois of the Chick Embryo for Virus Cultivation, Proc. Soc. Exper. Biol. & Med. **69**:341-345, 1948.

sq. cm. was applied to the chorioallantois, and the folded edges were straightened out. One drop of penicillin-streptomycin mixture was placed on each graft and the window closed with Scotch tape.[6] The egg was then placed in a bacteriologic

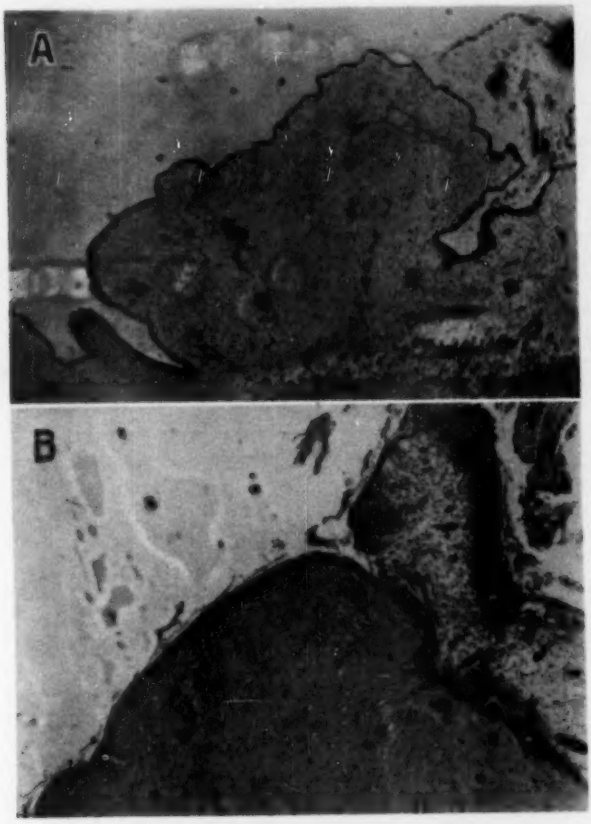

Fig. 2.—*A*, microscopic section of conjunctival graft. *B*, microscropic section of corneal graft, showing fusion of membrane to graft; duration, five days.

incubator maintained at 37 C. Through the window the graft was observed every day with the naked eye.

In transplanting the cornea, the routine procedure was to cut it off in its full thickness at the limbus and to spread it on the chorioallantois with the epithelium facing upward. In some experiments, however, only the superficial layers of the cornea were taken, as is done in lamellar keratoplasty.

Inoculation with the viruses was usually performed from 24 to 36 hours after grafting. A drop of a solution containing the virus of vaccinia or herpes simplex was applied directly to the surface of the graft after careful scarification.

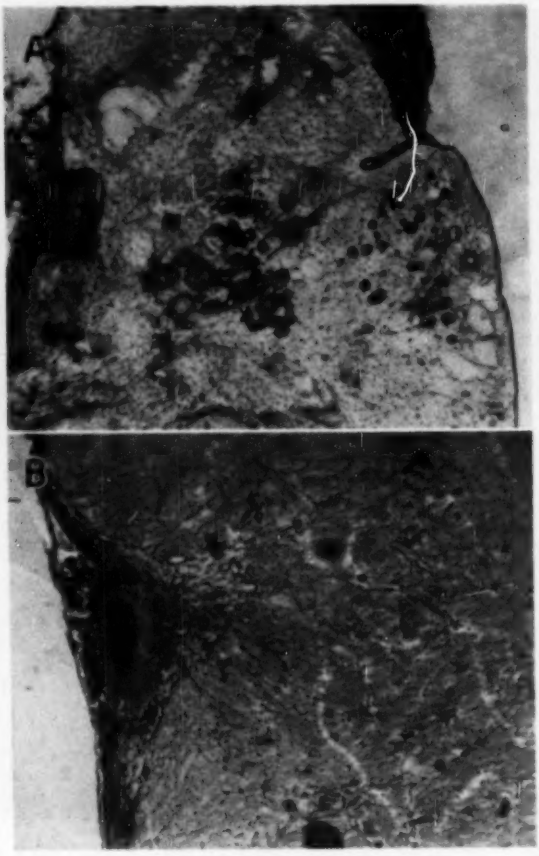

Fig. 3.—*A*, rabbit cornea eight days after grafting, showing invasion by vessels from membrane. *B*, rabbit cornea four days after grafting, showing good take and no exudate.

EXPERIMENTAL RESULTS

Twenty-four hours after the application of the conjunctiva or cornea to the membrane, the grafts became lightly adherent. Chick leukocytes frequently infiltrated parts of the graft. On the third day the vessels of

the grafted conjunctiva were filled with chick erythrocytes, and blood vessels were seen to invade the stroma of the cornea. The invading vessels penetrated deep into the graft on the succeeding eight days.

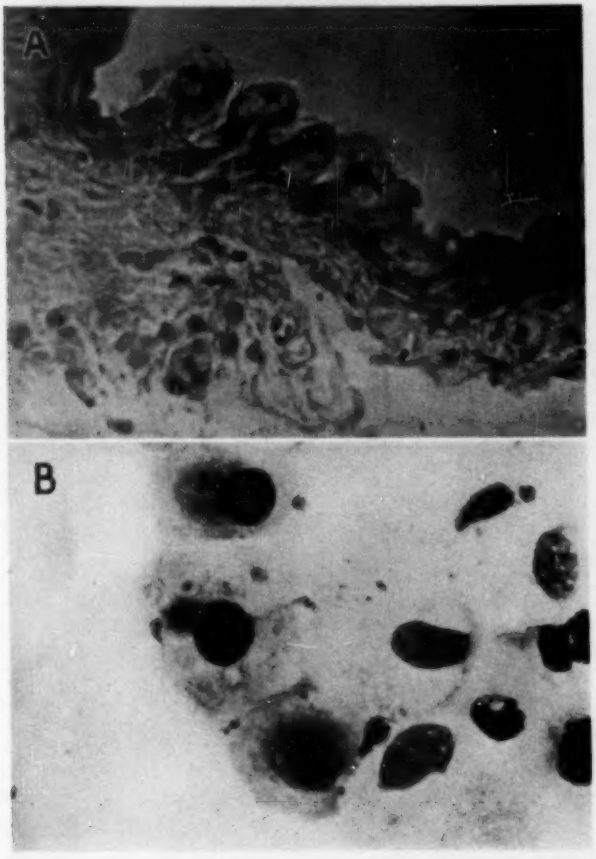

Fig. 4.—*A*, rabbit conjunctival graft infected with herpes simplex virus. Fifth regraft; duration, third day of the fifth regraft. *B*, scraping from rabbit corneal graft infected with vaccinia virus. Fourth regraft; duration, third day of fourth regraft.

Fusion of the graft with the membrane ultimately became complete. The corneal and conjunctival epithelia were well preserved, although

occasionally some of the superficial cells showed a tendency to desquamate.

Fig. 5.—Experimental herpetic keratitis produced in a rabbit by inoculation from corneal graft infected with herpes simplex virus. Fourth regraft; duration, third day of fourth regraft.

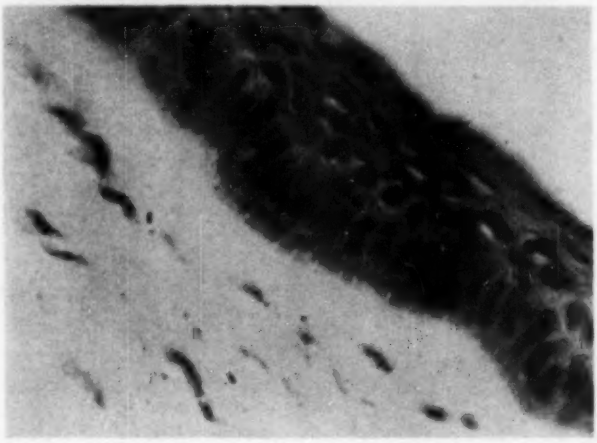

Fig. 6.—Corneal epithelium from experimental herpetic keratitis in a rabbit, produced by inoculation from infected corneal graft with herpes simplex virus (fig. 5).

Inoculation of the grafts with the viruses of vaccinia and herpes simplex gave rise to epithelial hyperplasia. The cytoplasm and nuclei

of the epithelial cells were swollen and contained, according to the virus, either intracytoplasmic or intranuclear acidophilic inclusions.

Grafted conjunctiva and cornea were removed from the first implantation and regrafted on a second embryo. This regrafting was carried successfully through five passages. Material from the fifth transfer of corneal graft, which had been infected with herpes simplex virus, was inoculated into the cornea of a rabbit and gave rise to keratoconjunctivitis after an incubation period of three days. The experimental disease was transferred successfully to new rabbits. The grafts were never left for more than four days on any one egg membrane, but with five regrafts they were maintained for as long as 20 days in some instances.

COMMENT

These experiments provided acceptable evidence that the conjunctiva and cornea can be transplanted successfully to the chorioallantoic membrane of the developing chick embryo. In the first days of the transplantation the "plasmotic circulation" maintains the nourishment of the graft, and on the third or fourth day the capillaries begin to grow from the membrane into the graft. Eventually the vessels penetrate deeply and invade the stroma, making it almost impossible to remove and regraft the transplanted tissue. In order to obtain successful regrafts, one must remove the grafted cornea or conjunctiva within the first three days, i. e., during the period of the "plasmotic circulation." Grafting the cornea with its whole thickness is to be preferred, in order that the new vascular organization may be delayed.

CONCLUSIONS

1. Rabbit conjunctiva and rabbit cornea can be transplanted to the chorioallantoic membrane of the developing chick embryo.

2. The transplanted conjunctiva and cornea can be regrafted at least five times.

3. Grafted and regrafted conjunctiva and cornea are capable of supporting the growth of the viruses of vaccinia and herpes simplex.

4. The viruses of vaccinia and herpes simplex develop intracellular inclusion bodies on the grafted conjunctiva and cornea and can produce experimental keratitis in the rabbit eye.

LOCALIZATION OF LESIONS CAUSING HORNER'S SYNDROME

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BROOKLYN

THE LESIONS which can cause the Horner syndrome are so numerous and widespread that they are important in every medical and surgical specialty. In many instances the signs and symptoms associated with the Horner syndrome give the physician and surgeon an exact insight into the nature and localization of the disease process. However, in far too many instances the etiologic process remains obscure because of a paucity of other helpful symptoms.

An attempt is made in this paper to provide a system for localization of lesions causing the Horner syndrome. In addition, the numerous lesions responsible will be outlined. Considering the anatomic relations of the sympathetic chain involved, it is no wonder that so many systems may be implicated in association with interruption of the chain.

There is increasing evidence that there exist autonomic centers in the cortex. Barris [1] demonstrated constriction of the pupil on stimulation of the peristriate area (Brodmann's area 19) of the cat, while Parsons [2] stimulated areas in the frontal lobe associated with ocular movements (Brodmann's area) and obtained dilation of the pupil and widening of the palpebral fissures. The former is a parasympathetic response, while the latter are sympathetic. Other investigators have shown vasomotor, lacrimal, pilomotor and gastrointestinal activity as a result of stimulation of various parts of the cortex.

The true autonomic centers, in the strictest sense, are situated in the hypothalamus. Many now consider that these are under the control of the cortical centers. Both sympathetic and parasympathetic activity have been adequately demonstrated by use of the Horsley-Clarke apparatus. It appears that there exist important connections between the hypothalamus and the midbrain. These constitute a sympathetic pathway the function of which is to inhibit the activity of the oculomotor nerve nucleus.

1. Barris, R. W.: Pupillo-Constrictor Area in the Cerebral Cortex of the Cat and Its Relationship to the Pretectal Area, J. Comp. Neurol. **63**:353-368, 1936.

2. Parsons, J. H.: On Dilatation of the Pupil from Stimulation of the Cortex Cerebri, J. Physiol. **26**:366-379, 1900-1901.

The exact course of most of the central sympathetic fibers is not yet known. However, it has been fairly well established from animal experimentation and clinical observation in man that the sympathetic fibers pass down from the hypothalamus ventral to the posterior commissure and divide, in the midbrain, into two portions. One part descends in the posterior longitudinal bundle. The other, with which this study is mainly concerned, enters the lateral portion of the midbrain and passes down in the recticular formation of the pons and medulla, from which it gains the anterolateral columns of the cervical portion of the cord. At the level of the seventh or eighth cervical or the first thoracic segment, a synapse is made. This is known as the ciliospinal center of Budge. It marks the termination of the first neuron, often referred to as the central neuron. At no time does the sympathetic chain cross over. It remains homolateral and unilateral throughout its course.

The second neuron enters the neck and ascends in the cervical portion of the sympathetic chain. The latter contains three ganglions, named according to their situation, i. e., the inferior, middle and superior. The particular fibers which are responsible for the signs and symptoms of the Horner syndrome pass through the inferior and middle ganglions and synapse in the superior cervical ganglion. This neuron is the second, or preganglionic.

Postganglionic fibers proceed from the superior ganglion and consist of two main plexuses, the internal carotid plexus and the cavernous plexus. The pupillary fibers arise mainly from the former. They accompany the nasociliary nerve and then the two long ciliary nerves to a plexus in the vicinity of the ciliary body, from which they course to the dilator muscle. They may also supply the ciliary muscle.[3]

THE HORNER SYNDROME

The syndrome bears the name of Horner,[4] who described it in 1869. However, Claude Bernard [5] first made reference to it in 1852. It consists of the following components:

Miosis.—The pupillary constriction is greatest, according to Walsh,[6] when the lesion is in the root of the seventh or eighth cervical or the first thoracic nerve. The miosis is said to be less pronounced if the

3. Cogan, D. G.: Accommodation and the Autonomic Nervous System, Arch. Ophth. **18**:739-760 (Nov.) 1937.

4. Horner, F.: Über eine Form von Ptosis, Klin. Monatsbl. f. Augenh. **7**:193-198, 1869.

5. Bernard, C.: Recherches expérimentales sur le grand sympathique et specialment sur l'influence que le section de ce nerf exerce sur la chaleur animal, Compt. rend. Soc. de biol. **5**:277, 1853.

6. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins, 1946, p. 188.

sympathetic chain is interrupted between the inferior and the superior ganglion. Maximum constriction is present only immediately after the sympathetic nerve is sectioned. After several days the pupil becomes somewhat larger and is more labile.[7] This behavior is explained by Cannon's law of denervation.[8]

When in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated.

This means that once the effector cells of the iris (the dilator fibers) become sensitized, as a result of denervation, minimal amounts of epinephrine in the blood stream will evoke maximal responses from the cells. Consequently, stimuli which cause changes in the *milieu interieur* will dilate the small pupil to a greater extent than the normal pupil. The time

Fig. 1.—Cat with postganglionic sympathectomy on the right side subjected to ether fumes (From Jaffe, N.: Am. J. Ophth. **32**:1683 [Dec.] 1949). The miotic right pupil became larger than the left, in accordance with the law of denervation. The entire black area represents the pupil.

required for this sensitization to occur in man is two to four days. In a series of 13 cats on which postganglionic sympathectomies were performed,[7] the dilator fibers required an average of three days for sensitization. When a preganglionic sympathectomy was performed, the denervation phenomenon also occurred. However, sensitization is about twice as great after a postganglionic sympathectomy.[9] Figure 1 is a photograph

7. Jaffe, N. S.: Practical Application of the Denervated Iris, Arch. Ophth. **40**:317-325 (Sept.) 1948.

8. Cannon, W. B.: Law of Denervation, Hughlings Jackson Memorial Lecture, Am. J. M. Sc. **198**:737-750, 1939.

9. Jaffe,[7] Hampel, C. W.: Effect of Denervation on Sensitivity to Adenine of Smooth Muscle in the Nictitating Membrane of the Cat, Am. J. Physiol. **111**:611-621, 1935.

of a cat's eyes after postganglionic sympathectomy during the excitement stage of ether anesthesia. The right, or sympathectomized, pupil is larger, owing to liberation of epinephrine. This is the so-called paradoxical pupillary dilatation. Consequently, the pupil is smallest before sensitization occurs. After the time required for sensitization has elapsed (three days), the pupil with the preganglionic lesion is smaller, since the sensitization is less. Some have attributed the later dilation of the small pupil to regeneration of the sympathetic nerve fibers. This is not likely, since when 3 cm. of the preganglionic cervical chain was removed in a cat the pupil became larger again after four days. This was certainly due to the denervation phenomenon.

Ptosis.—The ptosis seen with sympathetic paralysis is by no means as extensive as that seen with levator paralysis. There is an appreciable representation of smooth muscle in the lower lid, so that the latter is slightly elevated, while the upper lid is somewhat depressed.

Whereas the pupillary constriction is a constant feature of the Horner syndrome, ptosis is not. With lesions of the first neuron, especially the more central ones, there is likely to be no ptosis whatsoever. The cause of this dissociation is not clear. It may be assumed that in the formatio reticularis the fibers are more freely dispersed. Moreover, the pupillary dilator fibers are possibly more sensitive. This is the case in the optic nerve, where the afferent pupillary fibers are more sensitive than the visual fibers.

Enophthalmos.—I have never observed enophthalmos due to sympathetic interruption in man. Walsh and Sloan [10] observed several patients who were subjected to cervical sympathectomy when this procedure was in vogue in the treatment of pigmentary degeneration of the retina; they noted no enophthalmos. It appears that the enophthalmos is more apparent than real, owing to the paralysis of the smooth muscle of the lids. One would not expect retraction of the globe, since, as Whitnall [11] has observed, there are practically no smooth muscle fibers in the human orbit. In animals, however, there is an appreciable amount of smooth muscle in the orbit—hence a measurable degree of enophthalmos. I have produced exophthalmos in cats previously subjected to postganglionic sympathectomy by exciting them with ether (denervation phenomenon).

Ocular Hypotony.—There is much controversy concerning this feature. In animals it was shown that there is an immediate drop in tension following cervical sympathectomy, whether preganglionic or

10. Walsh, F. B., and Sloan, L. L.: Results of Cervical Sympathectomy in Pigmentary Degeneration of the Retina, Arch. Ophth. **14**:699-714 (Nov.) 1935.

11. Whitnall, S. E.: Anatomy of the Human Orbit and Accessory Organs of Vision, ed. 2, London, Oxford University Press, 1932.

postganglionic.[12] The hypotony is only temporary; a return to normal occurs in two days. The fall in pressure amounted to 5 to 7 mm. It was probably due to paralysis of the smooth muscle of the lids, globe and orbit. The return to normal may be due to the accompanying vasodilatation, caused by the elimination of the sympathetic tonus.

Anhidrosis.—There is no sweating on the ipsilateral side of the face and neck. This is usually obvious. The fibers for sweating leave those for miosis and ptosis shortly after the synapse in the superior cervical ganglion. The former accompany the external carotid artery, while the latter accompany the internal carotid artery. This sign has definite localizing value, since lesions involving the internal carotid or cavernous plexus cause a Horner syndrome without anhidrosis.

Transitory Rise in Facial Temperature.—When the patient is relaxed, the ipsilateral side of the face is warm and flushed. At other times, owing to the sensitization phenomenon, the face may be cold and pale.

In the early days of sympathetic nerve surgery, a postganglionic sympathectomy was performed for Raynaud's vasospastic disease. Owing to the sensitization of effector cells, the procedure resulted in failure. At times the pain was worse than before. Now a preganglionic sympathectomy is done, since the sensitization is mild and is far outweighed by the vasodilatation.

Depigmentation of the Iris.—Especially in patients with dark irises, lesions of the sympathetic chain may, in rare instances, result in depigmentation of the iris. This abnormality is most likely to develop in infants up to the age of 1½ years, at which age pigmentation is almost complete. Heterochromia iridis has been associated with Klumpke's paralysis (spinal birth injury). There are also reports of depigmentation associated with sympathetic lesions in adults. These, however, are exceedingly rare.

Secretion of Tears.—There is at present considerable controversy concerning the nervous control of weeping. An increase in the flow of tears following resection of the sympathetic chain has been noted by some [13] and a decrease by others.[14] According to Wilbrand and Saenger,[15] the sympathetic fibers govern normal secretion, while the parasympathetic fibers (via the facial nerve) control a copious flow of tears. This statement has been disputed.

12. Jaffe, N. S.: Sympathetic Nervous System and Intraocular Pressure, Am. J. Ophth. **31**:1597-1603, 1948.

13. Schiff, A.: Über zwei Fälle von intramedullären Rückenmarkstumoren, Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **2**:137-157, 1894.

14. Schirmer, O.: Über den Einfluss des Sympathicus auf die Funktion der Tränendrüse, Arch. f. d. ges. Physiol. **126**:351-370, 1909.

15. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges: Ein Handbuch für Nerven- und Augenärzte, Wiesbaden, J. F. Bergmann, 1901, vol. 2.

Other Signs.—Other, occasionally associated signs are facial hemiatrophy, cataract formation [16] and increase in amplitude of accommodation.[5]

LOCALIZATION OF LESIONS

Localization of lesions causing Horner's syndrome may be accomplished by two methods: (*a*) tests which determine at which level the sympathetic chain is interrupted, and (*b*) evaluation of signs and symptoms attributed to involvement of neighboring structures.

TESTS TO DETERMINE LEVEL OF INTERRUPTION

Reaction to Cocaine.—The use of cocaine is the most important and practical test for integrity of the sympathetic nerves. With lesions of the second and third neurons (from the center of Budge, in the cord, to the dilator fibers in the iris), cocaine causes practically no dilation of the pupil. If the lesion is only partial, it will cause a slight dilation, but much less than in the normal pupil.

It is known that cocaine potentiates the action of epinephrine. Its exact mode of action is still undetermined. It may produce its effect by inhibiting amine oxidase, thus permitting the epinephrine liberated at the nerve endings to act. If the sympathetic nerve is cut, no epinephrine is liberated; consequently, cocaine becomes impotent. For reasons which are not yet clear, cocaine does dilate the pupil when the lesion is central (first neuron). This requires further investigation. Thus, in Horner's syndrome due to a lesion in the thorax, neck or along the internal carotid artery the pupil does not dilate in response to cocaine.

The test is performed as follows: One drop of 4 per cent cocaine hydrochloride is instilled in each conjunctival sac at three minute intervals for three applications. The pupils are observed every 15 minutes for 45 minutes. The contrast is striking, and no special magnifying apparatus is required to view the results.

Reaction to Epinephrine.—Epinephrine when instilled in the conjunctival sac has no effect on the normal pupil. Immediately after sympathetic nerve section it also is without action. However, after the effector cells have become sensitized (following denervation), there is a pronounced reaction.

Epinephrine will exert its greatest effect when the lesion is between the superior cervical ganglion and the dilator fibers in the iris (postganglionic or third neuron). When the lesion is in the second neuron, i. e., between the center of Budge, in the cord, and the superior cervical ganglion, in the upper part of the neck, epinephrine has a less potent action. It will be remembered that sensitivity with such a lesion is about

16. Duke-Elder, W. S.: Text-Book of Ophthalmology, London, Henry Kimpton, 1949, vol. 4.

one-half that seen after postganglionic sympathectomy. In lesions of the first neuron, i. e., between the hypothalamus and the center of Budge, epinephrine usually has no effect on the pupil. This is by no means certain, however, as will be shown later.

The dilation obtained with epinephrine in postganglionic lesions is maximal. It is a very reliable test. However, for first and second neuron lesions the test is not as reliable.

The test is performed by placing 1 drop of epinephrine hydrochloride (1:1,000) in each eye every three minutes for three instillations and observing the pupil for 45 minutes. Ordinarily, the test is done in conjunction with the cocaine test. Forty-five minutes after the first instilla-

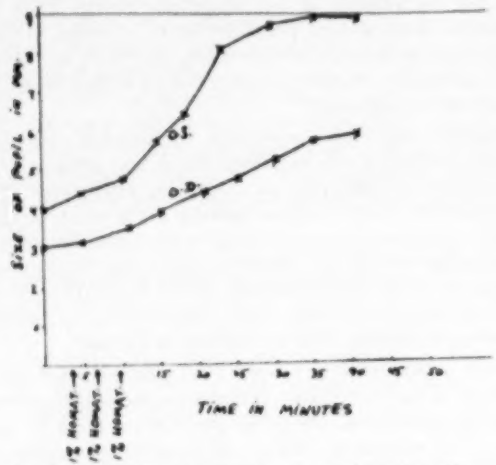

Fig. 2.—Reaction of pupils to homatropine in a patient with a Horner syndrome on the right. The normal left pupil dilated 5 mm.; the right pupil, only 3 mm.

tion of cocaine, if no, or only slight, dilation has occurred, epinephrine is placed in the eyes.

The following combinations are possible:

No reaction to cocaine; strong epinephrine reaction—lesion of the third neuron.
No reaction to cocaine; mild epinephrine reaction—lesion of the second neuron.
Good reaction to cocaine—lesion of the first neuron.

Homatropine Test.—Homatropine acts by blocking parasympathetic stimulation, thereby allowing the sympathetic fibers to exert their effect unopposed. In a Horner syndrome, the sympathetic tone of the iris is poor or nil. Thus, homatropine will dilate the pupil poorly. This effect is striking as compared with the response on the normal side. The test gives the same results no matter which neuron is interrupted (fig. 2).

Atropine Test.—This test is used in lesions of the third nerve to determine whether there is simultaneous involvement of the sympathetic fibers. With lesions of the third nerve, especially when incomplete, atropine causes further dilation of the already dilated pupil. However, if the sympathetic fibers are also involved, as is not infrequently the case, the pupil undergoes no further dilation with atropine.

Differentiation of the Miosis of Horner's Syndrome and an Irritative Miosis.—In the former the pupil retains its ability to react to light, while in the latter it does not. Cocaine does not dilate the pupil in either condition. Atropine causes a subnormal response with the Horner syndrome but a good reaction with irritative miosis. On the other hand, physostigmine gives a good response with the Horner syndrome but practically none with irritative miosis.

Psychosensory Reflex.—This is the only test included which is not pharmacologic. Walsh [9] stated that the psychosensory reflex, such as the reaction to pinprick or loud noise, is unaltered in Horner's syndrome. Foerster and Gagel [17] stated that it was unaltered in lesions of the second and third neurons but was exaggerated in lesions of the first neuron. Ury and Gellhorn [18] have maintained that reflex psychosensory dilation has nothing to do with the peripheral sympathetic nerves, occurring strictly with inhibition of the third nerve.

Nevertheless, it was shown [19] that lesions of the peripheral sympathetic fibers abolish about 80 per cent of the psychosensory dilation (fig. 3). Two factors are probably associated with normal pupillodilation in response to a noise or pinprick. One is peripheral sympathetic stimulation, and the other is central inhibition of the third nerve nucleus. Both proceed by pathways from the hypothalamus after cortical stimulation.

The cause of the conflicting opinions probably rests in the failure to recognize the denervation phenomenon. If a patient with a postganglionic sympathetic lesion (even preganglionic, but to a less degree) is subjected to a stimulus of sufficient magnitude as to cause liberation of epinephrine into the blood stream, the pupil will dilate markedly, owing to the action of the epinephrine liberated on the denervated nerve endings. This is a hormonal response. It was further shown in a cat with a postganglionic sympathectomy that excitation with ether will cause the pupil to dilate in about six seconds. The response was eliminated when the animal was adrenalectomized. In the same animal the pupil on the normal side dilated

17. Foerster, O.; Gagel, O., and Mahoney, W.: Über die Anatomie, Physiologie und Pathologie der Pupillarinnervation. Verhandl. d. deutsch. Gesellsch. f. inn. Med. **48**:386-398, 1936.

18. Ury, B., and Gellhorn, E.: Role of Sympathetic System in Reflex Dilatation of Pupil, J. Neurophysiol. **2**:268-275, 1939.

19. Jaffe, N. S.: True Psychosensory Dilatation and Delayed Psychosensory Dilatation of the Pupil, Am. J. Ophth. **32**:1681-1687, 1949.

immediately in response to the stimulation with ether. This is the "true psychosensory reflex." It is entirely nervous in origin and requires for its manifestation only the time necessary for the passage of the impulse along the nerve routes. The other reaction was termed "delayed psychosensory reflex." It is hormonal and requires the time for the liberation of the epinephrine into the blood stream and its flow to the dilator fibers of the iris.

Proponents of the theory that the psychosensory reflex is due solely to inhibition of the third nerve point out that in complete third nerve paralysis the reaction is abolished. However, in complete third nerve paralysis uncomplicated by associated sympathetic paralysis, the pupil is so widely dilated that practically no further dilation is possible.

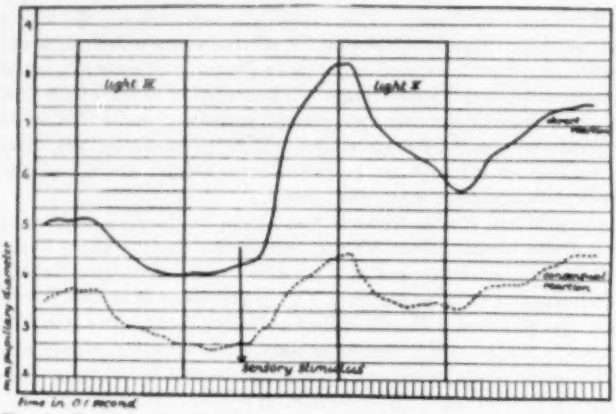

Fig. 3.—Psychosensory reflex. Note the striking difference in response to a sensory stimulus (crack of a gun) in the normal pupil (solid line) and in the sympathectomized pupil (dotted line).

Unlike the pharmacologic tests, the psychosensory reflex test requires a special apparatus and technic known as pupillography. In summary, a peripheral sympathetic lesion abolishes about 80 per cent of the "true psychosensory reflex."

Electric Skin Resistance.—Work in this field has been done largely by Richter.[20] It is well known that the resistance of skin to an electric current is greater when the skin is dry. Consequently, in a Horner syndrome there is an elevated electric skin resistance, due to anhidrosis. In cases of lesions peripheral to the separation of pupillary and sweat

20. Richter, C. P., and Woodruff, B. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, Surgery **10**:957-970, 1941.

fibers the test is of little value. Richter, using his method, was able to map out all areas of the skin devoid of sympathetic nerve supply by a measure of skin resistance.

LOCALIZATION OF SYMPATHETIC LESIONS BY EVALUATION OF SIGNS AND SYMPTOMS ATTRIBUTED TO INVOLVEMENT OF NEIGHBORING STRUCTURES

First Neuron.—A. Hypothalamus and Neighboring Structures: Lesions of the hypothalamus are not well understood. Many symptom complexes are possible in diencephalic lesions. Among the more important ones are (*a*) diabetes insipidus, (*b*) disturbance of temperature regulation, (*c*) disturbance of sleep regulation, (*d*) the adiposogenital syndrome and (*e*) the autonomic epilepsy of Penfield.[21]

1. Basal meningitis: The association of isolated cranial nerve paralysis, changes in the spinal fluid, papilledema or optic nerve atrophy, any of the hypothalamic symptom complexes, positive serologic reactions (not necessary) or meningeal signs (not necessary) is indicative of basal meningitis. Syphilis is the most frequent cause.

2. Pituitary tumor: Changes in visual fields, enlargement of the sella, hypophysial signs and optic nerve atrophy represent the well known pituitary syndrome.

3. Tumor of the third ventricle: By elevation of intracranial pressure, hypothalamic symptoms may occur. The tumor may extend laterally to produce a homonymous hemianopsia. Extension posteriorly may give rise to the pineal syndrome (dilated, fixed pupils and paralysis of upward or downward gaze). Lutz[22] stated that a binasal hemianopsia should suggest tumor of the third ventricle. This defect probably occurs through the tumor pushing the lateral aspect of the optic nerve against the carotid artery.

Other adjacent structures may become involved, accounting for pyramidal and extrapyramidal signs.

B. Brain Stem and Cord: 1. Midbrain: Here, again, little is understood concerning the clinical picture of sympathetic paralysis. By far the most frequent disease of the midbrain is syphilis. This accounts for the alterations in the pupillary reflex to light. Some have attributed the small pupil associated with the Argyll Robertson phenomenon to involvement of the sympathetic fibers. Others consider this disorder a chronic irritative miosis. The controversy is too complex and baffling for discussion here.

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21. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358-374 (Aug.) 1929.

22. Lutz, A.: Light Pupillary Reflex: Its Path and Abolition, Arch. Ophth. **47**:266 (May) 1918.

2. Pons: A tumor of the pons may be associated with a small pupil. An intrapontile hemorrhage may also cause miosis. There may be paralysis of conjugate eye movements, facial palsy (usually peripheral), sixth nerve paralysis, pyramidal tract signs and occasional eighth nerve signs. Ptosis is often absent. Included here are the Foville, Millard-Gubler and Raymond syndromes.

3. Medulla: When syringomyelia extends cephalad to involve the medulla, it is spoken of as syringobulbia. A large cavity is produced in the center of the spinal cord and the medulla. There is extensive proliferation of glial tissue. The tongue becomes paralyzed and atrophic. The patient becomes hoarse and cannot swallow (nucleus ambiguus). There is loss of pain and temperature sensations on the ipsilateral side of the face, due to involvement of the descending branch of the trigeminal nerve. Paralysis of the sixth nerve results in monocular convergent squint. The Horner syndrome may or may not be complete. Pupillary narrowing is constant, but ptosis and anhidrosis may be present only partially.

There are a number of medullary syndromes of definite localizing value. The Babinski-Nageotte syndrome consists of the Horner syndrome, hemiataxia, contralateral disturbance of pain and temperature sensations, nystagmus and contralateral hemiparesis. Wallenberg's syndrome is similar, except that there is involvement of the nucleus ambiguus (hoarseness and dysphagia). There are no signs referable to the pyramidal tract. The usual lesion causing this disorder is thrombosis of the posterior inferior cerebellar artery, which results in a wedge-shaped infarct of the medulla. The most frequent etiologic factor is syphilis. The Cestan-Chenais syndrome is a combination of the Babinski-Nageotte syndrome and the Avellis syndrome (glossopharyngeal or pharyngolaryngeal paralysis).

Multiple sclerosis and encephalitis may also give rise to medullary signs and symptoms.

4. Cervical portion of cord: (*a*) Syringomyelia. This is one of the most frequent general causes of the Horner syndrome in general. It is the commonest lesion of the cord resulting in this syndrome. There is extensive proliferation of the glia, with subsequent breakdown of this tissue to form a large cavity or multiple cavities. Often the first sign is loss of pain and temperature sensations over the lower parts of the body, due to involvement of the spinothalamic tract in the cord. Loss of proprioception and ataxia result as the posterior columns become involved. The anterior horn cells become implicated and result in flaccid paralysis and atrophy. The pyramidal tracts may become involved later, causing spastic paralysis. There may be ulcerations on the fingers, and the nails may show trophic changes. When Horner's syndrome is present, it is usually complete.

(*b*) Tumor and injury. Signs and symptoms caused by tumors and injuries vary according to the site of the insult. The diagnosis is made from the history, symptoms referable to the spinal cord and roentgenologic findings. The Horner syndrome is a common accompaniment.

(*c*) Tabes. Spinal tabes results in a characteristic clinical picture. Horner's syndrome is usually complete.

(*d*) Poliomyelitis. This disease may result in a variety of signs and symptoms, according to the area most severely involved. Ptosis may be due to poliomyelitis involving the cerebrum, the brain stem or the spinal cord. Third nerve paralysis due to lesions of the cerebral hemispheres or the brain stem (midbrain) may produce ptosis. Paralysis of the sympathetic fibers causes ptosis in lesions of the spinal cord and, less probably, in lesions of the brain stem. The size of the pupil associated with the ptosis is the distinguishing factor.

(*e*) Meningitis. This may also give rise to a Horner syndrome.

In the above conditions, lesions were of the first sympathetic neuron. The Horner syndrome was usually incomplete. It tended to become more complete with descent into the cervical portion of the cord. In all cases miosis was the constant feature.

Second Neuron.—Spinal Birth Injury: Injury to the lower fibers of the brachial plexus results in Klumpke's paralysis. If the injury is proximal to the point of departure of the white rami communicantes, a Horner syndrome results. Heterochromia iridis on the side of the injury is a characteristic feature. Normal pigmentation of the iris appears to be associated in some way with the integrity of the cervical sympathetic nervous system. Pigmentation of the iris is not complete until the age of 2 years. Frequently, in Klumpke's paralysis associated with Horner's syndrome the homolateral iris remains relatively depigmented. In some cases pigmentation finally becomes normal; in others there remain patches of depigmentation; in others the iris is completely depigmented.

Cervical Rib: In this condition, a supernumerary rib arises from the seventh cervical vertebra on one or both sides. The signs are usually limited to the arm. There is often pain on the ulnar side of the forearm. Changes in sensation are common. When the anomaly encroaches on the lower cords of the brachial plexus, a Horner syndrome ensues.

There are numerous other causes of second neuron lesions. The site of the lesion may be in the thorax or the neck.

Thoracic Lesions: Lesions in the lung apex: Tuberculosis may lodge in the apex of the lung and thus cause pressure on the cervical sympathetic chain. Carcinoma of the apex of the lung, the so-called Pancoast tumor, is often first suspected from the development of a Horner syndrome.

Aneurysm: Aneurysm may occur in the aorta or the subclavian or carotid artery and may encroach on the sympathetic fibers. The commonest lesion of this type is seen in cardiovascular syphilis, occasionally resulting in a large aneurysmal dilatation of the ascending aorta.

Enlarged Mediastinal Glands or Tumors: These may occur in Hodgkin's disease, leukemia, lymphosarcoma and tuberculosis. Similarly, such lesions in the neck may result in a Horner syndrome.

Lesions of the Neck: Enlargement of the thyroid: In most cases the enlargement of the thyroid is obvious. However, a small lesion in the lateral lobe of the gland occasionally escapes observation. Such a lesion may be a calculus or cyst. Adenoma, adenocarcinoma and the various types of goiters are more readily discovered.

Lymphadenopathy of Any Origin: This is an especially frequent cause. However, it escapes notice too easily. It is surprising that a Horner syndrome of this origin is not commoner. In most persons large lymph nodules may be found directly on the sympathetic chain. In none of the 28 animals referred to above was there absence of lymphadenopathy along the sympathetic chain. The commonest cause of an enlarged node is tuberculosis.

Carcinoma of the Esophagus: The dysphagia and other symptoms are usually well advanced by the time the Horner syndrome develops.

Other Causes: Less common causes in the neck are neuroma of the sympathetic chain, aneurysms of the branches of the carotid artery and retropharyngeal tumors.

Third Neuron.—Lesions of the third neuron are considerably less common than those of the first or second neuron.

Aneurysms of the Internal Carotid Artery or Branches: This is probably the most frequent cause of lesions of the third neuron. The associated symptoms depend on the site of the aneurysm. Several groups of symptoms may arise.

(*a*) Paratrigeminal syndrome: Aneurysmal dilatation or actual aneurysm of the internal carotid artery in the neighborhood of the gasserian ganglion gives rise to miosis, slight ptosis, pain in the distribution of the trigeminal nerve and weakness of the muscles of mastication. Sweating is intact.

(*b*) Cavernous sinus syndrome: Aneurysm of the internal carotid artery in the cavernous sinus results in severe pain in the eye and supraorbital region and paralysis of the third and possibly the fourth and sixth, nerves. The sympathetic cavernous fibers of the plexus are also involved. There is no loss of sweating. To prove that the sympathetic fibers are also involved in the presence of a third nerve paralysis, the atropine test is used. The homolateral pupil does not dilate as much as the normal one, since there is loss of sympathetic tonus. As a rule, the

sympathetic involvement is overshadowed by the third nerve paralysis frequently associated with carotid aneurysm.

Tumors of the Orbit: Usually the growth is in the region of the superior orbital fissure. Again, there is simultaneous involvement of the sympathetic and the parasympathetic system.

Other Causes: A number of rare instances of Horner's syndrome due to unusual lesions have gained the literature.

A case of Horner's syndrome due to laceration of the sympathetic fibers during tonsillectomy was reported by Hammer.[23] A case of extension of suppurative otitis media to involve the internal carotid sympathetic plexus was cited by Metzner and Wölfflin.[24] Passow [25] pointed out the association of Horner's syndrome with scleroderma and facial hemiatrophy. Bing [26] observed Horner's syndrome with chlorosis and other forms of anemia. The presence of Horner's syndrome with lesions of the sigmoid flexure and rectum is known as Thies's sign. It is little understood.

REPORT OF CASES

Several cases are reported to illustrate the technic outlined above. These also serve to show the wide anatomic range of lesions which may cause the Horner syndrome.

CASE 1.—L. B., a Puerto Rican man aged 38, was first seen at the City Hospital clinic complaining of pain over the left eye of one day's duration. Vision was 20/20 in each eye. The left pupil measured 3 mm. and the right pupil 4 mm. Gross reactions of the pupils to light and in near vision were normal. Intraocular tension was 18 mm. in the right eye and 15 mm. in the left eye. Funduscopic studies revealed slight arteriolar narrowing and a positive arteriolar-venule crossing sign.

The blood pressure on his admission to City Hospital was 210/110. Electrocardiographic examination revealed left axis deviation. The blood chemistry was normal. On the first hospital day the patient complained of a sharp pain in the left side of his face over the entire distribution of the trigeminal nerve. The clinical picture was that of trigeminal neuralgia with a typical "trigger" mechanism. Ptosis of the left eyelid was then obvious; it measured 3 mm. There was no enophthalmos. Sweating was active and equal on the two sides. The left pupil was smaller than the right. Four per cent cocaine hydrochloride was instilled into each eye every five minutes for three instillations. After 45 minutes the right pupil dilated from 4 to 9 mm., and the left pupil, from 3 to 4 mm. At the end of this time epinephrine hydrochloride (1:1,000) was instilled into each eye. There was no further dilatation of either pupil.

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23. Hammer, C.: Einseitiger Hornerscher Symptomenkomplex nach beiderseitiger Gaumenmandelausschälung, Klin. Monatsbl. f. Augenh. **90**:79-80, 1933.

24. Metzner, R., and Wölfflin, E.: Klinische und experimentelle Untersuchungen über Halssympathicuslähmung, Arch. f. Ophth. **89**:308-322, 1915.

25. Passow, A.: Hornersyndrom, Heterochromie und Status dysraphicus, ein Symptomenkomplex, Arch. f. Augenh. **107**:1-51, 1933.

26. Bing, R.: Gehirn und Auge, ed. 2, Munich, J. F. Bergmann, 1923.

The patient was placed on a regimen of bed rest, potassium thiocyanate and sedation. After five days the facial pain disappeared and the ptosis was practically gone. The left pupil, however, remained slightly smaller than the right. At the clinic, one month later, the left pupil responded normally to cocaine, but it remained smaller than the right.

This case falls into the group known as the paratrigeminal syndrome, described by Raeder.[27] It will be recalled that the postganglionic cervical sympathetic fibers reenter the skull along the internal carotid artery. Aneurysmal dilatation of the latter in the neighborhood of the gasserian ganglion accounts for the facial pain and the Horner syndrome. The presence of sweating is understood, since the fibers for sweating travel along the external carotid artery and have already left the branches which go to the eye (fig. 4).

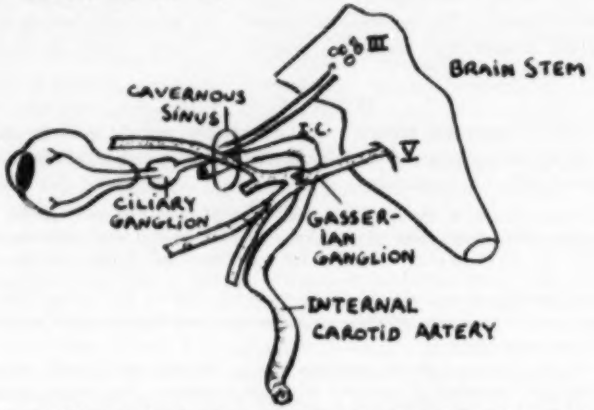


Fig. 4.—Diagram showing the proximity of the internal carotid artery to the gasserian ganglion before the artery enters the cavernous sinus. Aneurysmal dilatation of the artery with pressure on the ganglion may give rise to the paratrigeminal syndrome.

The absence of reaction of the left pupil to cocaine is typical of sympathetic paralysis. Ordinarily, a third neuron lesion, such as this, causes an exaggerated response to epinephrine. However, the test was performed two days after the onset of symptoms, a period insufficient for the dilator cells of the iris to become hypersensitive to epinephrine.

Case 2.—W. Z., a white Russian aged 62, was admitted to City Hospital complaining of progressive hoarseness and inability to swallow, of four days' duration. He also noticed that he was ataxic and fell usually to the left side. He had never been seriously ill before. He had been very active and worked

27. Raeder, J. G.: "Paratrigeminal" Paralysis of Oculo-Pupillary Sympathetic, Brain **47**:149-158, 1924.

hard as a laborer all his life. There was no history of operation. He had had syphilis twenty years previously and had received no treatment.

Physical examination revealed a well developed, well nourished white man. The following pertinent changes were noted: The right pupil was larger than the left, but both reacted well to light and in near vision. The fundi were normal. The prostate gland was moderately enlarged. There were inability to swallow, difficulty in speaking and depressed pharyngeal reflexes. There was hypesthesia of the right side of the body, including decreased sensitivity to touch, pain, temperature and vibration but normal stereognosis and position senses. The left side of the face showed decreased sensitivity to pain, temperature and touch. There was swaying to the left in the Romberg test. The finger to nose test was poorly performed on the left side, and a rebound phenomenon was elicited. There was rotatory nystagmus in a counterclockwise direction. During fluoroscopic examination, barium swallow welled up in the larynx and pyriform sinuses. It was promptly coughed up.

The blood pressure was 120/60. The urine was normal. The red cell count was 4,150,000; the hemoglobin content, 70 per cent, and the white cell count, 10,000, with 76 per cent segmented granulocytes. The erythrocyte sedimentation rate (Cutler method) was 29 mm. in one hour. The Mazzini test of the blood gave a negative reaction. The urea nitrogen of the blood measured 28 mg. per 100 cc. Electrocardiographic findings were within normal limits. Examination of the spinal fluid showed an initial pressure of 120 mm. of water; a globulin content of 51 mg. and a sugar content of 63 mg., per 100 cc.; a 4 plus Wassermann reaction, and a normal colloidal gold curve. The fluid contained 2 lymphocytes per cubic millimeter. Roentgenograms revealed nothing abnormal.

A pupillogram was taken at the Institute of Ophthalmology, Presbyterian Hospital, three weeks after the patient's admission to City Hospital. At this time his speech was much improved, but all other signs were present.

Psychosensory pupillary dilation was from 5.0 to 5.83 mm. on the right and from 4.0 to 4.25 mm. on the left. Thus, the reflex was considerably reduced on the left. The cocaine-epinephrine curve was atypical. Sensitivity was demonstrated, as the left pupil responded in an exaggerated fashion to epinephrine. The reaction to cocaine was better on the right (fig. 5).

The patient was fed intravenously and by Levin tube until eight weeks after admission, when he began to swallow normally.

It was immediately evident that this case represented a thrombosis of the left posterior cerebellar artery (Wallenberg syndrome). The lesion was in the pontobulbar transition region. Horner's syndrome was due to involvement of the descending sympathetic fibers in the formatio reticularis; the left hemiasynergia, to involvement of the left restiforme body (inferior cerebellar peduncle); hypesthesia of the right side of the body, to involvement of the left spinothalamic tract; hypesthesia of the left side of the face, to implication of the left descending branch of the trigeminal nerve, and rotatory nystagmus, to a lesion of the left Deiters nucleus. Dysphagia and hoarseness were the result of involvement of the nucleus ambiguus.

Case 3.—G. S., a white German aged 63, was admitted to City Hospital complaining of dyspnea. He had been admitted previously for herniorrhaphy on the right side in 1944 and for repair of bilateral Dupuytren contracture in 1945.

Physical examination revealed a well developed, well nourished white man. He became dyspneic after speaking for several seconds or after moderate activity. Ophthalmologic examination revealed the following signs: The left pupil measured 4 mm., and the right pupil 2.5 mm., in diameter. Both reacted well to light and in near vision. There was partial ptosis of the right eyelid, measuring 4 mm. Levator function was normal. The fundi were normal.

With the aid of pupillography, the reactions of the pupils to a psychosensory stimulus (crack of a gun) were determined. The normal pupil (left) dilated from 4.75 to 6.33 mm.; the miotic pupil (right), from 3.67 to 4.12 mm. The response of the sympathectomized pupil was only 28 per cent of that of the normal pupil.

The blood pressure was 148/88. The heart sounds were of good quality, and there was regular sinus rhythm. Fluoroscopic studies revealed a normal-sized

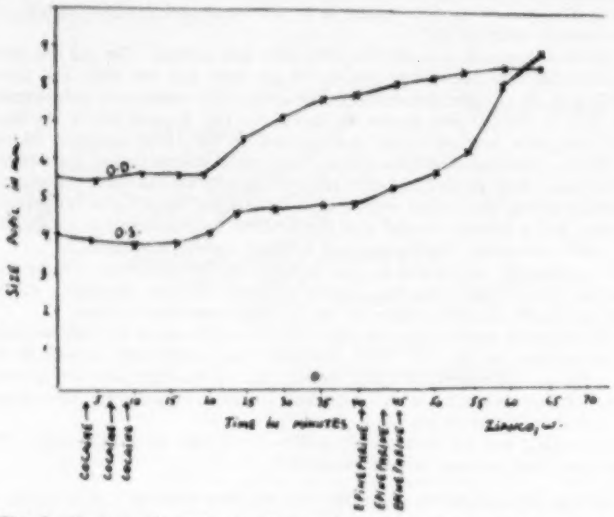


Fig. 5.—Cocaine-epinephrine test in a patient with a lesion of the first sympathetic neuron. Note that the normal (right) pupil dilates with cocaine, while the denervated left pupil does not. The latter, however, responds in an exaggerated fashion to epinephrine. This response is atypical.

heart. The Mazzini reaction of the blood was negative. An electrocardiogram was normal. The blood chemistry was normal.

A roentgenogram of the chest revealed a 4 by 6 inch (10 by 15 cm.), oval area of calcific density in the upper right mediastinal region, this area displaced the trachea and compressed it (fig. 6). The impression was that of a calcified substernal adenoma of the right lobe of the thyroid gland. The mass was not palpable.

The presence of a Horner syndrome associated with dyspnea in a patient with normal cardiac function should lead one to suspect an obstructive lesion in the neck. The lesion here was in the second (preganglionic) neuron. The reactions to cocaine and the psychosensory dilation curve were typical of a peripheral sympathetic lesion (fig. 7).

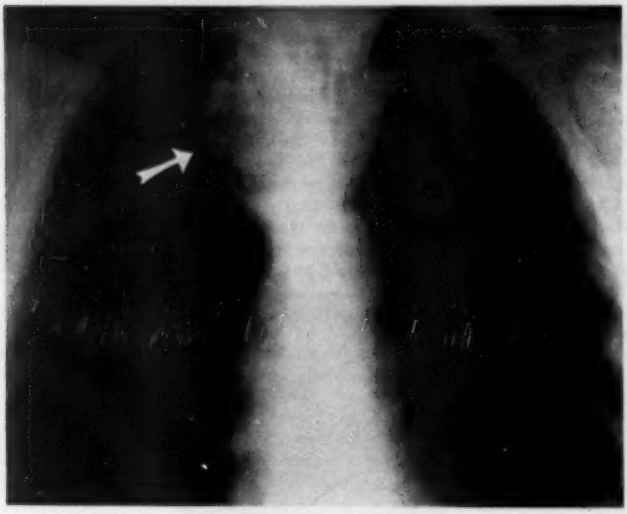


Fig. 6.—Roentgenographic demonstration of substernal calcified adenoma of the thyroid gland on the right side.

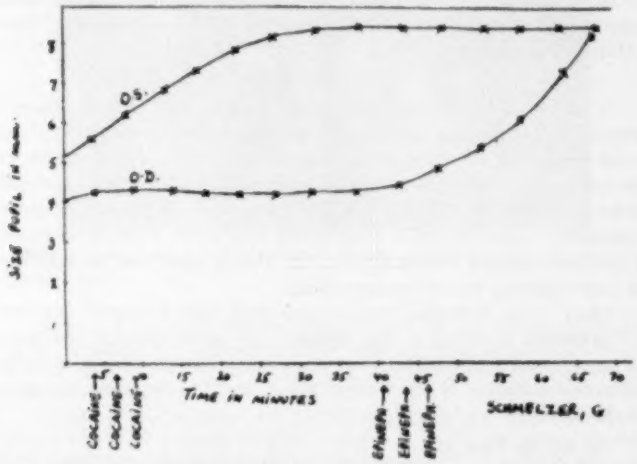


Fig. 7.—Cocaine-epinephrine test in a patient with a lesion of the second sympathetic neuron. The normal (left) pupil dilates with cocaine, while the denervated (right) pupil does not. The latter shows increased sensitivity to epinephrine.

CASE 4.—J. W., a Negro aged 59, was seen at the City Hospital clinic. He was under treatment in the cardiac division for syphilitic heart disease. He had first learned of his "bad blood" 30 years ago, while he lived in the South. He received a series of injections of arsenic and bismuth compounds on two occasions.

The patient had been in cardiac failure on several occasions. The serologic reactions of the blood had been negative since 1943. Serologic reactions of the spinal fluid had been negative since his treatment at the clinic (nine years before). The patient stated that he had had several spinal taps before this but had never known the results of the serologic tests.

Clinic records revealed that the patient has been hoarse since 1948. He had had a Horner syndrome for the past six months. Cardiac examination disclosed a systolic thrill palpable over the aortic area. On auscultation a rough systolic murmur was heard. The blood pressure was 210/65. The heart was considerably enlarged to the left.

Ophthalmologic examination revealed anisocoria of 1 mm. The right pupil measured 3 mm., and the left pupil, 4 mm. Both reacted well to light and in near vision. There was incomplete ptosis on the right side. Levator function was good. The fundi revealed moderate narrowing of the arterioles and the arteriolar-venule crossing phenomenon. There were no hemorrhages or "exudates." The disks were normal.

A cocaine-epinephrine test was performed. The left pupil dilated from 4 to 8.5 mm., and the right pupil from 3 to only 4.5 mm., at the end of 45 minutes. Epinephrine caused no further dilation of the left pupil but dilated the right pupil from 4.5 to 9.5 mm.

This case represents a typical lesion of the second neuron. The aneurysmal dilatation of the aorta was easily observed roentgenologically. In such cases the aneurysm points posteriorly and presses on the recurrent laryngeal nerve (hoarseness) and the cervical sympathetic fibers (Horner's syndrome).

SUMMARY

A system of localizing lesions which produce Horner's syndrome is presented. Localization may be accomplished by two methods: (*a*) tests which determine the level of the sympathetic lesion, among which are the reactions of the pupil to cocaine, epinephrine, homatropine, atropine and a psychosensory stimulus, and (*b*) evaluation of signs and symptoms attributed to involvement of neighboring structures. There is frequently a symptom complex associated with the Horner syndrome at each level of interruption of the sympathetic chain.

Cases of the following lesions associated with Horner's syndrome are presented to illustrate the method: (1) paratrigeminal syndrome; (2) syndrome of the posterior inferior cerebellar artery; (3) calcified substernal adenoma of the thyroid gland, and (4) syphilitic aneurysm of the aorta.

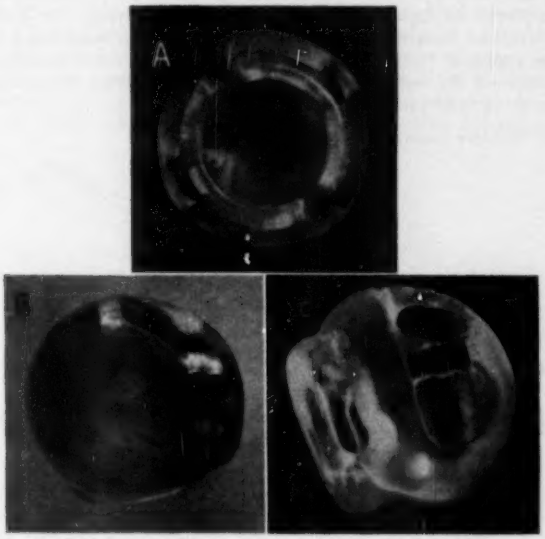
309 Sterling Place (17).

Clinical Notes

A NEW ORBITAL IMPLANT WHICH USES THE SIX EXTRINSIC MUSCLES

GEORGE P. LANDEGGER, M.D.
LOS ANGELES

A new covered implant which has all six extrinsic muscles attached to it is herewith presented. It is a modification of Dr. Orwyn Ellis' plastic implant, made of lucite.* It comes in two sizes, 18 by 18 and 16 by 16 mm., over-all dimensions. It weighs 2.94 Gm.



Orbital implant using the six extrinsic muscles. *A*, front view; *B*, rear view; *C*, lateral view.

There are two slots for the oblique muscles on the temporal side behind the equator of the implant. The slots run in a horizontal direction. In front of the equator there is a ring. Beneath are openings for the rectus muscles.

All the ocular muscles are preserved during the enucleation procedure, and 0000 chromic surgical sutures U. S. P. are passed through their insertions. The oblique muscles are passed through their respective slots first and tied onto each other behind the equator. The superior and inferior rectus muscles are passed through their respective openings beneath the ring in front and are tied to each other. The lateral rectus

muscles are also placed beneath the ring and are sewn onto each other. Tenon's capsule, which was preserved during the operative procedure, covers the implant with a running 0000 chromic surgical suture U. S. P. Black silk sutures close the conjunctiva.

The advantage of this implant is that the oblique muscles form a sling around it and push it slightly forward. In this way, the implant becomes more permanently placed in the center of the orbit, where it is supposed to be. Another advantage of having the oblique muscles attached to the implant is that the lower lid stays in its proper position and has no tendency to sag, as it sometimes does when an implant moves downward.

Twenty-four such implants have been put in by myself and other ophthalmic specialists on the Pacific Coast in the last two and one-half years, with very satisfactory results and good motion. The implant can be purchased through Storz Surgical Supply Company, St. Louis, or from Mr. Ted Keiser, Los Angeles. There is also available a motion picture, approved by the American College of Surgeons, demonstrating the technic of the surgical procedure and the insertion of the implant. It may be secured by writing me.

3875 Wilshire Boulevard, Los Angeles 5.

A FORCEPS FOR CORNEOSCLERAL SUTURES

PAUL TOWER, M.D.
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IN CATARACT extraction, placement of the corneoscleral sutures can be hastened and facilitated by slightly modifying the instrument ordinarily employed. Frequently the Burch pick is used; this ophthalmostat is provided with two fine and sharp points, as well as with stops near the tips, to prevent excessive penetration of episcleral tissue.

The essential features of this instrument can be easily adapted to a forceps designed for corneoscleral suturing. The jaws of these forceps measure 6.5 mm.; and into the distal third of the left blade are fused two needle-sharp, slightly inward curved teeth, measuring somewhat less than 1 mm. in length. The inner surfaces of the cross arms are corrugated

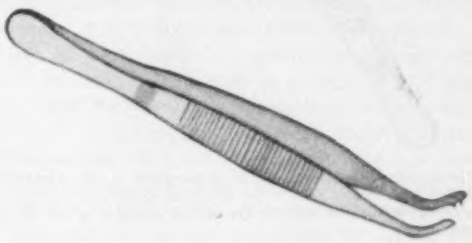

Fig. 1.—Two needle-sharp, slightly inward curved teeth are fused into the distal third of the left blade of a forceps. The inner surfaces of the cross arms are corrugated to serve as a needle holder.

in a crisscross pattern, as is usual in needle holders. Thus, the point of the needle carrying the scleral suture can be grasped firmly when it emerges from the sclera (fig. 1).

For scleral sutures, the instrument is placed on the sclera, and on slight pressure the point will engage the episcleral tissue. Then the suture needle is inserted and directed through the episcleral tissue so that its tip will come out between the blades of the forceps. On mere closure of arms, the instrument serves as a needle holder; the emerging portion of the needle is grasped, and the needle is pulled through the sclera. In this manner fixation of the globe, securing of the needle and manipulation through the sclera are accomplished with one instrument; thus, time is saved and the entire procedure simplified.

For corneal sutures, the instrument is inserted close to the corneoscleral limbus, thus fixing the sclera. As the outer of the two needle-sharp teeth is 2.5 mm. distant from the tip of the blade, the forceps can be made to reach well beyond the edge of the cornea (fig 2). The needle on the

corneal end of the double-armed suture is directed toward the region between the blades of the instrument. The forceps is then closed, engaging the needle, and the suture is pulled through the corneal tissue. Thus, no additional injury of the cornea occurs, as the teeth of the forceps remain fixed in the superficial layer of the sclera.

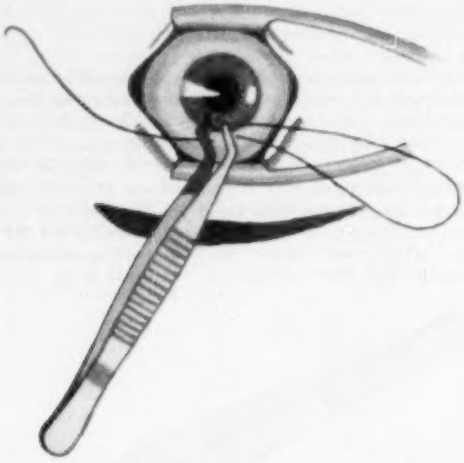

Fig. 2.—The corneoscleral suture has been preplaced in the sclera. The teeth of the left jaw of the forceps are fixed in the episcleral tissue close to the limbus. The forceps reaches well beyond the edge of the cornea, ready to grasp the point of the emerging suture needle.

The described forceps for corneoscleral sutures has been employed for some time and proved to possess considerable advantages. While especially designed to facilitate the placing of corneoscleral sutures, the instrument may also be used with benefit for all other types of scleral sutures.

610 South Broadway (14).

Annual Reviews

NEURO-OPHTHALMOLOGY

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A REVIEW of the publications on neuro-ophthalmology which have appeared during the past twelve months leaves one with the impression that the literature in this field is composed largely of unrelated and unexplained bits, mostly in the form of case reports. About half these publications contribute nothing new and will not be mentioned in this review. Abstracts of others may be pieced together to make more or less complete pictures. In addition, there are some outstanding contributions, several in the form of review articles by well known writers and investigators. These will be pointed out in the hope that the reader will peruse them in the original and in their entirety.

That much of the literature on neuro-ophthalmology concerns rare diseases of little clinical significance is an opinion held also by Leinfelder.[1] In a brief discussion of misconceptions in neuro-ophthalmology (which one wishes he had expanded to greater length), he calls erroneous the current impression that this field is difficult. He feels that knowledge of the gross anatomy of the brain and of the visual pathway and the oculomotor nerves is an adequate basis for interpretation. Edema of the optic disk, although it does not invariably accompany increased intracranial pressure, is an important diagnostic sign of it. Statistics of 25 years ago, still widely quoted, indicated that 80 per cent of patients who had brain tumor had choked disks. Diagnostic methods have so improved that brain tumors are now recognized earlier, and at present about 40 to 50 per cent of patients who have brain tumors have choked disks. He notes that regression of edema of the disks after operation is slow, as edema persists for two to three weeks. Admittedly, there is no constant rate of absorption for all patients, but in the experience of this reviewer it seems to be about 1 D. in each ten days for subacute papilledema, a little faster for the acute type and a little slower for the chronic type. A residual fulness may persist for many weeks. Leinfelder mentions, too, that the appearance of the nerve head does not always permit the diagnosis of optic nerve atrophy, as some nerve heads appear

From the Section on Ophthalmology, Mayo Clinic.

1. Leinfelder, P. J.: Misconceptions in Neuro-Ophthalmology, Wisconsin M. J. 49:297-298 (April) 1950.

pale but are normal. Pathologic pallor is the result of gliosis and constriction of capillaries. An estimate of the extent of optic nerve atrophy must be based on studies of the visual fields.

Perimetry has received attention in relatively few published papers, and yet these few merit consideration. Chamlin [2] urges that when a cerebral lesion is suspected, if a gross defect is not present, the fields should be explored for minimal defects with test objects smaller than those ordinarily employed. He recommends a 1 mm. bead on the tangent screen at 2 meters. He points out the importance of searching carefully on each side of the vertical meridian for small differences in visibility of the test object and states that a rapid comparison of the two sides may elicit differences. The differences may be in the level of the isopters, or there may be qualitative differences between the nasal and the temporal sides of the fields at comparable distances from the point of fixation, the object appearing clearer on one side than on the other. The breadth of field compared with the normal for the particular test object may be informative. Experienced perimetrists will agree with the author's thesis that targets in common use are too large for eliciting minimal defects in the fields, and they will concur in Chamlin's advice that fields be explored for minimal defects with small targets.

Zugsmith and Rehman [3] described a test object for perimetry which they claim gives more accurate and reliable results than the usual test objects. Their test object consists of a 6 volt straight filament bulb mounted at the end of an 18 inch (44.5 cm.) wand. It is used at a standard perimeter or tangent screen and produces a pulsating light in the form of a flash of measurable duration, which can be varied in intensity and in frequency. They have found that flashes, occurring at intervals of 1, ½, ⅓ and ¼ seconds, are optimal, and they have made provision for controlling the duration of the flash. Their technic is to move the light slowly from the periphery toward the fixation point and to record the point at which it appears. Their use of a pulsating light differs from that described by Miles.[4]

Miles [4] has begun publication of the work that he has been carrying out during recent years on flicker fusion frequency. He used an electronic flickering light with a lighted interval of 0.010 second and varied its frequency. The lamp was mounted in a reflector behind a paper-covered, orange white glass 13 cm. in diameter. The size of the target could be reduced to 0.5 cm. He found that with his equipment

2. Chamlin, M.: Minimal Defects in Visual Field Studies, Arch. Ophth. **42**: 126-139 (Aug.) 1949.

3. Zugsmith, G., and Rehman, I.: A Simple, More Accurate Means of Charting Visual Fields, Am. J. Ophth. **32**:1573-1576 (Nov.) 1949.

4. Miles, P. W.: Flicker Fusion Frequency in Amblyopia ex Anopsia, Am. J. Ophth. **32**:225-231 (June, pt. 2) 1949.

normal flicker fusion frequency was 45 flashes per second centrally and 50 flashes per second 8 degrees temporally. It varied over various parts of the retina but, unlike the results in field studies with usual targets, higher sensitivity was elicited at the periphery. He considered flicker fusion to be a primitive sensation received in the cortex of the brain in centers other than those involved in visual acuity or pattern fusion.

In cases of amblyopia ex anopsia the central area of the amblyopic eye performed like the peripheral retina, having a higher flicker fusion frequency than the central portion of the normal fellow eye. Miles thinks that this suggested suppression of the central cones. Advanced age in itself does not depress flicker fusion frequency.[5] It was depressed with decrease in pupillary diameter, but not if sufficient time was permitted for complete adaptation to the reduced illumination, a period of about two hours. Miles [6] tested a series of 24 eyes for which a diagnosis of early glaucoma had been reasonably well established and in which vision and fields were normal. He used a 5 cm. target at 0.5 or 1 meter on a tangent screen with a radius of 30 degrees and found defective flicker fusion frequency in every case, most commonly nasally. He had found previously that depression also occurred in sclerosis and degeneration of old age out of all proportion to loss of visual acuity and ordinary field changes. To the casual reader his charts are less informative than the customary charts based on standard technics. The most obvious criticism of this report is stated by the author himself:

> These preliminary case studies do not represent the ultimate in representations of field defects associated with glaucoma by flicker fusion frequency determinations. The technique and results will be certainly improved.

Ophthalmologists should watch for future reports from Miles, with the confident expectation that the research project he has set for himself will contribute a practical, sensitive technic to clinical perimetry.

In a report of studies on the occipital lobe, concerned with the significance of small areas of preserved central vision, Austin, Lewey and Grant [7] present six cases of occipital lobectomy. Preservation of central vision ranged from 0.25 to 1.5 degrees. The same degree of sparing was found in eight control patients who had chiasmal lesions and seemed to be present also in patients with lesions of the tract. Aus-

5. Miles, P. W.: Flicker Fusion Fields: I. The Effect of Age and Pupil Size, Am. J. Ophth. **33**:769-772 (May) 1950.

6. Miles, P. W.: Flicker Fusion Fields: III. Findings in Early Glaucoma, Arch. Ophth. **43**:661-677 (April) 1950.

7. Austin, G. M.; Lewey, F. H., and Grant, F. C.: Studies on the Occipital Lobe: I. Significance of Small Areas of Preserved Central Vision, Arch. Neurol. & Psychiat. **62**:204-221 (Aug.) 1949.

tin, Lewey and Grant feel that minimal eccentricity of the fovea with slight physiologic variation in fixation explains the results most satisfactorily.

Two cases of altitudinal hemianopsia, studied with unusual care and presented with unusual clarity, are reported by Berkley and Bussey.[8] In the first case, superior altitudinal hemianopsia followed a blow on the back of the head, without demonstrable skull fracture, as a result of bilateral damage to the lower lips of the calcarine fissure. In the second case, inferior altitudinal hemianopsia resulted from a shrapnel wound in the occipital area, through a bilateral destructive lesion involving the upper lips of the calcarine fissure. In the latter case, temporal crescents were preserved, and there was also preservation of the macula. Berkley and Bussey explain the macular preservation as due to the extensive representation of the macula in the calcarine area. In comparing these two cases, they point out the greater inconvenience to the patient when the visual loss is inferior, rather than superior.

One of the causes of sudden loss of vision in elderly people is "temporal arteritis." Bruce,[9] having occasion to report a case, brings the literature up to date and describes the nature of this disease. It attacks persons between the ages of 55 and 80 years and produces fever, malaise, anorexia and loss of weight. After a few days or months the temporal arteries become painful and tender, swollen and nodular. Pathologic examination shows thickening of all three coats; the intima is hypertrophied, and the media and adventitia are infiltrated with lymphocytes and segmented granulocytes. The media is necrotic and contains giant cells. The term "temporal arteritis" is a misnomer, for the disease is not limited to the arteries of the head but is widespread throughout the body. In 40 per cent of cases the eyes are involved by closure of the central retinal artery or one of its branches or by ischemia of the optic nerve behind the point of entry of the retinal vessels into the nerve. Often both eyes are affected. There is as yet no satisfactory treatment.

Reports of single cases of neuromyelitis optica (Devic's disease) continue to appear in print, and during the past year there were half a dozen more. Since the appearance of the paper by Stansbury,[10] in which he presents 5 cases of his own, with necropsy studies and a complete historical review of all published cases, other writers with a case to report may lose some of their urge to send it at once to an editor. Until some-

8. Berkley, W. L., and Bussey, F. R.: Altitudinal Hemianopia: Report of 2 Cases, Am. J. Ophth. **33**:593-600 (April) 1950.

9. Bruce, G. M.: Temporal Arteritis as a Cause of Blindness: Review of Literature and Report of a Case, Tr. Am. Ophth. Soc. **47**:300-316, 1949.

10. Stansbury, F. C.: Neuromyelitis Optica (Devic's Disease): Presentation of 5 Cases, with Pathologic Study and Review of the Literature, Arch. Ophth. **42**:292-335 (Sept.); 465-501 (Oct.) 1949.

one has a cause or cure for this affliction, Stansbury's thorough and noteworthy study deserves a high place in the literature on neuromyelitis optica. Briefly, the author concludes that the disease may occur at any age but is commonest between 30 and 50 years, it is more frequent in females than in males, the initial symptom is optic disability in half the cases and spinal disability in the other half, loss of vision occurs in both eyes, neurologic signs are variable but the myelitis is a rapidly ascending type, remissions occur in half the cases, and death is likely to occur in the first two years.

Gliomas of the optic nerves, too, are so uncommon that when they occur a report of the case is likely to find its way into print. Among the cases of glioma reported recently are the two by Horns,[11] in both of which an astrocytoma was present. One patient was a woman aged 41; the other, a boy aged 5 years. The author stated that 90 per cent of gliomas occur before the age of 20 and most of them before the age of 5 years. Loss of vision is the first symptom, and exophthalmos is the next. Gliomas of the optic nerve do not metastasize, but they tend to spread along the optic nerve and cause death by intracranial extension. Another case, reported in considerable detail, is that of Saebo.[12] His patient, a woman aged 43, for four months had noted diminution of vision of the left eye and protrusion of the globe. Examination showed that the left eye was amaurotic; it protruded forward 3 mm.; the optic disk was swollen and elevated 9 D.; the retinal vessels were engorged, and there were several retinal hemorrhages. The right eye appeared normal. Roentgenograms of the skull disclosed no abnormalities. During the next five months the left optic foramen widened, and intraocular pressure increased. The eye and optic nerve were then removed, and tissue from the optic nerve showed the presence of glioblastoma multiforme. The patient died a year later of cerebral extension of the tumor.

Glioma of the optic nerve may be difficult to diagnose early in its course. This was brought home to the reviewer by a patient he saw recently, a man aged 36, who complained of progressive loss of vision in the right eye of two months' duration. Diagnoses of optic neuritis and of choked disk had been made previously. Visual acuity was restricted to counting fingers with the right eye; the other eye was normal in every respect. The nerve head was elevated 6 D., and the retinal veins were engorged. The possibility of glioma of the optic nerve was discussed with associates and then discarded, because proptosis and limitation of

11. Horns, R. C.: Primary Tumors of the Optic Nerve: Report of 2 Cases of Glioma, Minnesota Med. **33**:241-243; 304 (March) 1950.

12. Saebo, J.: Primary Tumor of the Optic Nerve (Glioblastoma Multiforme), Brit. J. Ophth. **33**:701-708 (Nov.) 1949.

movement of the eye were not present; a tentative, unsatisfactory diagnosis of optic neuritis was made. After a few days of fever treatment the eye became completely blind, the disk was elevated 8 D. and stasis was visible in the retinal veins. Anticoagulant therapy, carried out over a period of several days, was without benefit. Then, two weeks after his admission, obvious limitation of gaze upward and downward, proptosis of 2 mm. and a paracentral scotoma in the previously unaffected (left) eye developed. Roentgenograms of the skull showed no enlargement of the optic canal. These findings were sufficient to warrant surgical exploration. Through a right transfrontal craniotomy opening, the optic nerve was explored and found to be enlarged to four times its usual diameter by a swelling which extended backward through the chiasm and into the optic tract. Biopsy disclosed the presence of a malignant astrocytoma. Roentgen therapy was advised.

Compression of the optic nerve and its differential diagnosis are discussed by Meadows [13] in connection with the presentation of 11 cases, seven of basal meningioma, three of aneurysm and one of glioma of the optic nerve and chiasm, with charts of the perimetric fields and drawings of the sites of the lesions. He calls attention to the usual absence of pain and headache in meningioma and to the usual appearance of severe pain early in the course of aneurysm, and mentions the unfortunate circumstance that early in the course of both these conditions roentgenography, ventriculography and arteriography may yield no evidence of disease. To be differentiated are retrobulbar neuritis and chiasmal arachnoiditis. So little is known about the latter that any diagnosis of it not based on inspection should be viewed with suspicion.

A rare cause of inferior altitudinal hemianopsia is the presence of fusiform aneurysm of the internal carotid artery beneath the anterior clinoid process. The lesion is generally bilateral and presses the optic nerves upward against the bony optic canals or the overlying anterior cerebral arteries. As described by Ley,[14] the walls of the aneurysm are irregular, with folds and cavities, and the lumen may be almost obliterated. Microscopically, hypoplasia of the muscularis and degeneration of the intima, with hyalinosis and calcification, may be noted. Ley recommends that surgical procedures be performed early, before optic nerve atrophy is severe, and that it consist of freeing the optic nerves by unroofing their canals and opening their dural sheaths. Oculomotor paralyses, in his experience, do not occur with these aneurysms. On the other hand, with the commoner saccular aneurysms there are subarachnoid hemorrhage, impairment of the oculomotor and trigeminal

13. Meadows, S. P.: Optic Nerve Compression and Its Differential Diagnosis, Proc. Roy. Soc. Med. **42**:1017-1034 (Dec.) 1949.

14. Ley, A.: Compression of the Optic Nerve by a Fusiform Aneurysm of the Carotid Artery, J. Neurol., Neurosurg. & Psychiat. **13**:75-86 (Feb.) 1950.

nerves and positive angiographic signs. Jaeger,[15] too, points out that an aneurysm of the latter type should be suspected when persistent orbital pain is associated with paresis of the third nerve.

Similarly, with aneurysm of the posterior communicating artery, according to a report of seven cases by Alpers and Schlezinger,[16] there was in most cases a history of pain, retro-orbital in location, often spreading to the side or the back of the head and persisting for one to several weeks, and usually oculomotor paralysis followed the onset of pain after an interval of a few hours or days. In a few instances paralysis of the trochlear nerve was associated. The headache and ocular paralysis were on the same side as the aneurysm. It is the opinion expressed by these authors that aneurysms of the posterior communicating artery are usually small and accessible and consequently a favorable type for surgical treatment, the object of ligation being to prevent rupture. In one case spontaneous rupture and death occurred before operation was undertaken. Surgical measures were carried out in the other six cases and were reported as successful in four; that is, the patient survived the operation. In only one case was there return of function of the oculomotor nerve. No statement was made concerning the relief of pain.

Hyaline bodies (or drüsen) on the optic disks are likely to lead the unwary into diagnostic difficulties, for these bodies may be responsible for an appearance resembling chronic papilledema. Furthermore, they may produce defects in the visual fields which also resemble those of chronic papilledema. A period of careful observation over a few weeks or months should demonstrate a definite change in cases of papilledema and little or no change in cases of hyaline bodies. Three noteworthy reports of this condition have been published within the period covered by this review. Chamlin and Davidoff[17] report nine cases, several of which had been diagnostic problems from the neurosurgical standpoint. Their colored illustrations, unfortunately, are inferior reproductions of originally excellent fundus photographs. François[18] presents detailed studies of six cases with sketches of the optic disks, charts of the visual fields showing contractions and arcuate

15. Jaeger, R.: Aneurysm of the Intracranial Carotid Artery: Syndrome of Frontal Headache with Oculomotor Nerve Paralysis, J. A. M. A. **142**:304-309 (Feb. 4) 1950.

16. Alpers, B. J., and Schlezinger, N. S.: Aneurysm of the Posterior Communicating Artery, Arch. Ophth. **42**:353-364 (Oct.) 1949.

17. Chamlin, M., and Davidoff, L. M.: Drusen of Optic Nerve Simulating Papilledema, J. Neurosurg. **7**:70-78 (Jan.) 1950.

18. François, P.: Les verrucosités hyalines de la papille, Ann. d'ocul. **182**: 249-278 (April) 1949.

scotomas and a long bibliography. Törnquist [19] reports three cases with defects in the fields. His first case is of greatest interest and importance in that visual fields were charted and found to be normal at the first examination and during a two year period of observation scotomas appeared and increased. None of these authors sheds any new light on the pathogenesis of this condition.

Syphilis deserves and has continued to receive its full share of comment, especially in regard to therapy. In a commendable review, Klauder and Meyer [20] observe that syphilitic optic nerve atrophy occurs in association with all forms of neurosyphilis and that it is seen most frequently with tabes or the tabetic form of dementia paralytica. They found the average interval between infection and onset of atrophy of the optic nerve to be eighteen years. In their series of patients with optic nerve atrophy the most constant findings were pupillary abnormalities and positive serologic reactions of the blood and spinal fluid for syphilis. The pupillary abnormalities were among the earliest and most constant signs of neurosyphilis, preceding by years the appearance of subjective symptoms. Without entering into the argument themselves, they note that there is no agreement among pathologists as to the relation, if any, between the inflammatory changes in the margins of the optic nerves and the degenerative process. They refer to Bruetsch's description of an inflammatory process in the intracranial portion of the optic nerves as preceding atrophy of the nerve fibers and observe that in the inflammatory stage the optic nerves are amenable to antisyphilitic therapy and that the fields may improve under it. Igersheimer [21] states that, contrary to the opinion expressed by Bruetsch, the descending optic nerve atrophy of basilar syphilitic meningitis is not like that of dementia paralytica or of tabes. In the latter conditions the pathologic process always starts in the marginal zone, near the pial sheath, either near the globe or in any part of the optic nerve. In the earliest stages there is degeneration without exudation. The pathologic process consists in structural and chemical changes in the glial system and disappearance of capillaries, which are the cause of the degeneration of the nerve fibers. Responsible for these changes are undetermined toxins of the Treponema. Antisyphilitic drugs have no arresting effect on the atrophy. Much the same opinion is expressed by Blatt [22] in his report of 387 cases of tabetic atrophy of the optic nerves. He showed that malaria had an unfavorable

19. Törnquist, R.: On Hyaline Bodies (Drusen) as the Cause of Atrophy of the Optic Nerve, Acta ophth. **27**:1-9, 1949.

20. Klauder, J. V., and Meyer, G. P.: Early Diagnosis of Syphilitic Primary Optic Nerve Atrophy, Arch. Ophth. **43**:537-552 (March) 1950.

21. Igersheimer, J.: Atrophy of the Optic Nerve in Tabes and Dementia Paralytica, Arch. Ophth. **42**:170-177 (Aug.) 1949.

22. Blatt, N.: La valeur de la malaria-thérapie dans l'atrophie syphilitique des nerfs optiques, Ann. d'ocul. **182**:513-520 (July) 1949.

effect and that vitamins and rest were more beneficial than arsenicals. He is careful to point out, however, that these results are to be distinguished from the favorable results of malarial therapy in dementia paralytica uncomplicated by tabes.

Penicillin is recommended for the treatment of early syphilis by Harrington and Henry,[23] especially of syphilitic uveitis and optic neuritis. They warn that it may give rise to the Herxheimer reaction and that consequently small doses of the drug are advisable in early stages of therapy. They are less enthusiastic about its use for interstitial keratitis and yet consider it the treatment of choice because other measures are even less effective.

During the past year several reports dealing with special aspects of disturbances of ocular motility have been published. Henderson,[24] of the University of Michigan, reinvestigated the arrangement within the oculomotor nuclei and arrived at results which fail to confirm the work of Bender and Weinstein and tend to support the older conceptions. He concludes that the arrangement within the oculomotor nuclei is such that impulses for elevating the eyes and raising the upper lids arise in the rostral portions of the oculomotor nuclei and that the impulses for turning the eyes downward take origin in the more caudal portions. Experimental work on the monkey showed that a distinct pattern of cortical localization exists in both area 17 (the striate visual cortex) and area 19 (the parastriate visual cortex), which can be related anatomically and functionally to the more primitive arrangement in the midbrain. Fiber pathways from area 17 pass forward to the tectum of the midbrain in a layer just outside the visual radiations. Pathways from the upper calcarine area reach the caudal portions of the tectum, and those from the lower calcarine area terminate in the more rostral portions. Thus, the superior visual field relates to the rostral portion of the oculomotor nucleus, and the inferior field, to the caudal portion of the oculomotor nucleus. Fibers passing forward from the parastriate cortex of area 19 terminate in the tectum in an arrangement the reverse of that of visual area 17, an arrangement that Henderson does not regard as inconsistent, because he found short association bundles connecting the lower part of area 17 with the upper part of area 19 and vice versa.

Cogan and Loeb [25] studied the optokinetic response of patients with intracranial lesions. They used a rotating drum 8 inches (20.3 cm.) in diameter; on the outer cover of the cylinder were pasted black

23. Harrington, D. O., and Henry, R. W.: Present Concept of the Therapy of Ocular Syphilis, Am. J. Ophth. **32**:806-812 (June, pt. 1) 1949.

24. Henderson, J. W.: The Anatomic Basis for Certain Reflex and Automatic Eye Movements, Am. J. Ophth. **32**:232-238 (June, pt. 2) 1949.

25. Cogan, D. G., and Loeb, D. R.: Optokinetic Response and Intracranial Lesions, Arch. Neurol. & Psychiat. **61**:183-187 (Feb.) 1949.

figures 3 inches (7.6 cm.) in height (diamonds, hearts, clubs and spades). Optokinetic response was interpreted as abnormal when on rotation of the drum in two directions there was a difference in response that was grossly evident and constantly present. Also considered as abnormal were those cases in which no response could be elicited in either direction. Cogan and Loeb tested a series of 90 patients with proved cerebral disease and found abnormal responses in 58. For nine patients it was the sole ocular abnormality. That it was not dependent on involvement of the visual pathways was demonstrated by its presence in 18 patients who showed no hemianopsia. It was found with lesions of the middle, posterior or anterior portions of the cerebrum. The authors concluded that it had localizing value, for the optokinetic response was defective on rotation of the drum to the side of the lesion.

Falls, Kruse and Cotterman[26] report three cases of the Marcus Gunn phenomenon in two generations—those of a boy, his mother and his mother's brother. In the first two patients it had been noted during nursing soon after birth. In the boy there was slight ptosis of the left upper lid with retraction of this lid on opening or on protruding the jaw but not on deviating the jaw to either side. The mother had slight ptosis of the right upper lid, and the lid retracted on chewing and on protruding the jaw but not on lateral deviation. The uncle, who had not been aware of the condition, exhibited barely perceptible ptosis of the right upper lid, slight retraction on ordinary chewing and elevation of the lid of 2 to 3 mm. on protruding the mandible. There was no elevation on lateral movement of the jaw. The phenomenon was inherited in this family as an irregular dominant. Falls, Kruse and Cotterman commented that a satisfactory explanation of the Marcus Gunn phenomenon is lacking.

Myasthenia gravis accounted for paralysis of the extraocular muscles in two cases reported by Lisman.[27] Signs of the disease were localized to the eyes, and the diagnosis was not apparent until the injection of neostigmine. Even though the author has nothing new to offer, he does well in calling attention to this entity, which deserves serious consideration in the diagnosis of any disorder of extraocular muscles when pupillary reactions are normal. Ptosis of the upper lid and weakness of elevation of the globe are frequently seen early, but there are exceptions. The reviewer has seen it in a case of isolated paralysis of a lateral rectus muscle which he diagnosed as being due to involvement of the sixth nerve, and he was made to suffer his full share of chagrin by a colleague who relieved the condition by an injection of neostigmine.

26. Falls, H. F.; Kruse, W. T., and Cotterman, C. W.: Three Cases of Marcus Gunn Phenomenon in Two Generations, Am. J. Ophth. **32**:53-59 (June, pt. 2) 1949.

27. Lisman, J. V.: Ocular Myasthenia Gravis, Am. J. Ophth. **32**:565-571 (April) 1949.

Oculomotor nerve paralysis was observed by Bardram [28] in seven of 90 cases of verified adenomas of the pituitary gland, a frequency which seems remarkably high. He noted that with aneurysm it is more frequent, often of sudden onset and accompanied with pain.

Bilateral total ophthalmoplegia occurred in two cases of adenoma of the pituitary gland, as reported by Walsh.[29] In his first case, one of acromegaly, there had been bleeding into the tumor, followed by excruciating pain in the head and bilateral total ophthalmoplegia. After removal of part of the tumor, the ophthalmoplegia disappeared, and the fields returned to normal. In his second case, blindness and ophthalmoplegia had begun suddenly. After operation the ophthalmoplegia disappeared, but the patient remained blind. The article is illustrated by excellent anatomic diagrams and is written with the authority and clarity that have made Walsh a popular writer and teacher.

Tuberous sclerosis occurred in three siblings, aged 10, 8 and 2 years, according to a report by Miles and Dixon.[30] All three patients exhibited retinal lesions, radiopaque areas in the brain, abnormal electroencephalograms and epileptiform seizures. The two older children had adenoma sebaceum, and the boy, aged 8 years, was mentally retarded. There was no history of the disease in other members of the family. The calcified lesions in the brain, which were visible roentgenographically, when viewed through a stereoscope, were seen to lie in close relation to the lateral ventricle. Miles and Dixon point out that the scattered radiopaque lesions of toxoplasmosis ordinarily do not lie near the lateral ventricles. This point could prove helpful in differential diagnosis.

Two noteworthy review articles have appeared during the past year—"Migraine and Its Ocular Manifestations," written by Donahue [31] as a thesis for the American Ophthalmological Society, and "Trauma to the Head with Particular Reference to Ocular Signs," by King and Walsh.[32] The latter contains a comprehensive discussion of head trauma; of injuries to the optic nerves, cerebral hemispheres and brain stem, and of the sources of arteriovenous fistulas and intracranial bleeding. This is not the place to abstract an article of such length. Let the interested reader consult it himself, for he will find it concisely written and full of information.

28. Bardram, M. T.: Oculomotor Pareses and Non-Paretic Diplopia in Pituitary Adenoma, Acta ophth. **27**:225-258, 1949.

29. Walsh, F. B.: Bilateral Total Ophthalmoplegia with Adenoma of the Pituitary Gland: Report of 2 Cases; an Anatomic Study, Arch. Ophth. **42**:646-654 (Nov.) 1949.

30. Miles, P. W., and Dixon, J. M.: Tuberous Sclerosis in 3 Siblings, Arch. Ophth. **41**:473-480 (April) 1949.

31. Donahue, H. C.: Migraine and Its Ocular Manifestations, Arch. Ophth. **43**:96-141 (Jan.) 1950; Tr. Am. Ophth. Soc. **47**:554-605, 1949.

32. King, A. B., and Walsh, F. B.: Trauma to the Head with Particular Reference to Ocular Signs, Am. J. Ophth. **32**:191-206 (Feb.); 379-398 (March) 1949.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Wendell L. Hughes, M.D., Chairman

Isadore Givner, M.D., Secretary

Regular Meeting, May 16, 1949

CLINICAL PRESENTATIONS

A Sr^{90} Beta Ray Applicator for the Eye. DR. CHARLES I. THOMAS, Cleveland (by invitation).

Sr ^{90} is the radioactive element that results from the breakdown of uranium, and together with its daughter element yttrium, it supplies a good source of long, half-life, strong beta rays. The applicator presented was made under the direction of Dr. H. L. Friedell, professor of radiology at Western Reserve University, with the assistance of Mr. J. Krohmer, radiological physicist at the Atomic Energy Laboratory located at Western Reserve University.

This applicator was developed for three reasons: (1) that a source of well controlled and standardized beta rays might be available, (2) that radiation therapy might be safe for the personnel dealing with the bulb and (3) that the bulb would not have to be filled at frequent intervals.

Strontium chloride was obtained in the liquid state, and an apparatus was constructed which allowed the solution to drop into the lucite®-lined aluminum bulb. Each drop was concentrated and crystallized by evaporation, hastened by the passage of clean, dry, warm air over the surface of this liquid. A total of 16.5 ml. was used, and the assay was 13 millicuries per milliliter. A lead casing ⅛ inch (0.32 cm.) in thickness encloses the aluminum bulb which reaches to a distance of ¼ inch (0.64 cm.) from the free end. This applicator has had a 22 year half-life.

Standardization was carried out by studying the penetration on x-ray plates and, clinically, by comparing the reactions in skin tests with those obtained by using the radon bulb. The extrapolation chamber yielded a value of 5.3 r per second, which is believed to be within an accuracy of 10 per cent. The strontium bulb has been used for some time, and its results are comparable to those obtained with the radon bulb.

PAPERS OF THE EVENING

Early Diagnosis of Sarcoma of the Choroid. DR. ADALBERT FUCHS (by invitation).

First symptoms of sarcoma of the choroid may be slight visual disturbance, photopsia, metamorphopsia, micropsia and scotoma. Formerly one assumed that brownish or grayish patches represented a melanosarcoma. Now it is known that pigmented sarcoma of the choroid may

produce large white patches, sometimes with retinitic spots, and even of irregular outline. This occurrence as a rule is noted when the tumor originates at the posterior pole, where the tendency to retinal detachment is less than anteriorly.

Prior to appearance of the subjective symptoms, an anomaly of refraction may draw attention to the possibility of sarcoma. A patient of middle age had hypermetropia of 2 D. in one eye which he could not compensate for with his accommodation for distance, but with 2 D. he had normal vision. The fundus was normal. The eye was enucleated for sarcoma a year later.

In the stage of detachment one must differentiate between the solid and the serous detachment. There are two important anatomic features. In addition to the visible detachment, a large minimal detachment surrounds the raised serous detachment. Clinically, in such a case one finds a much larger defect in the visual field than would be expected from the ophthalmoscopic picture. Perimetric measurement of such a visual field has to be done with a 1 cm. test mark. In the case of beginning sarcoma the second important feature is a very tiny detachment near the ora serrata opposite the tumor. Such a detachment can sometimes be seen clinically by the appearance of an invisible area in a tesselated fundus or by the defect in the visual field. Such a detachment is very frequent. In the case of beginning sarcoma tonometry does not show increased tension as a rule, but the tension may become considerably higher if it is measured 24 hours after homatropinization.

Of greatest importance is transcleral illumination. Duke-Elder's illustration shows the pigmentation of an eye with a blue iris; as a rule, the iris does not show transparent slits, and the ciliary body appears rather dark and not very bright, as shown in Arruga's illustration. The ciliary body is sometimes so pigmented that considerably less light passes through it than at the equator. In normal eyes, if the uveal pigmentation is intense, transillumination may reveal nothing significant. Control inspection of the fellow eye will confirm this fact. Transillumination is especially valuable when one can change the intensity of the light; then one may find slight differences in the illuminated pupil on applying the lamp to different parts of the sclera. Abundant hemorrhage in the vitreous or an old subretinal hemorrhage may hinder the transscleral illumination. Leukosarcoma may be entirely transilluminable; this tumor is not as rare as indicated by Martin Jones (1946), who found only 26 cases of leukosarcoma in the literature. Leukosarcoma is far too frequent to justify the publication of a case. As a rule, a detachment due to tumor does not show a tear, but a tear or a tear-shaped small hemorrhage in the outermost periphery may be present, so that a tear is not a proof that there is no sarcoma.

In the stage of absolute glaucoma, the diagnosis of a tumor is frequently not made. Dr. J. H. Krug, of the New York Eye and Ear Infirmary, found anatomically verified tumors in 6 per cent of 377 eyes which were enucleated for absolute glaucoma; 4 per cent of these tumors had not been diagnosed. It is advisable to transilluminate the globe in every case of absolute glaucoma when one cannot get information on the fundus.

Mucormycosis of the Eye: Report of a Case. Dr. W. Conrad Stone (by invitation).

A case of mucormycosis of the eye and orbit, in a Negro aged 42, who died in the Presbyterian Hospital, New York, was presented. The diagnosis was diabetes mellitus, acute meningoencephalitis, partial thrombosis of the left cavernous sinus and uremia. A species of the fungus Mucor was identified by its characteristics in material from the brain meninges and ocular tissues, although cultures were not obtained. The pathological findings in the posterior section of the left eye were discussed and photomicrographs shown. The literature was briefly reviewed and the association of uncontrolled diabetes mellitus, orbital cellulitis and acute meningoencephalitis was emphasized.

Diagnostic Sign in Allergic Conjunctivitis: Dr. J. L. Malbran and Dr. G. P. Halberg (by invitation).

To evaluate pathological changes in the punctum lacrimale, 100 so-called normal subjects were examined, and the lower punctum lacrimale was measured in both eyes by means of a calibrated eyepiece of the Goldman slit lamp. The scatter graph of the so-called normal subjects showed that the normal average diameter of the punctum lacrimale is between 0.2 and 0.3 mm. In patients with allergic conjunctival disorders, such as hay fever, vernal conjunctivitis, chemical allergy and others, the average diameter of the punctum lacrimale increases.

The authors stated the opinion that this increase in diameter of the punctum lacrimale could be used as a diagnostic sign in allergic conjunctivitis. Fluorescein staining showed diminished drainage of the lacrimal fluid and a bubble in the dilated punctum. In trying to explain this peculiar phenomenon, the authors inclined to the hypothesis that the constrictor muscle of the punctum lacrimale loses its tonus, probably as a result of paretic or paralytic factors.

Slit lamp views of the normal and pathological punctum lacrimale, scatter graphs and a histological section of the lacrimal apparatus were shown.

Nodular Iritis Due to Sarcoidosis: Report of Four Cases. Dr. Leo Esbin, Brooklyn (by invitation).

Four cases of nodular iritis due to sarcoidosis were reported. The condition was observed in young Negroes, and the lesions ranged from small miliary nodules of the Koeppe variety to large lobulated masses on and in the iris. One patient had uveoparotid fever, and in the remaining three cases pathological material of either the skin or a lymph node was an aid in diagnosis, the sections revealing typical hard tubercles without caseation.

In all cases the reaction to the intradermal tuberculin test was negative, the albumin-globulin ratio was altered and no tubercle bacilli were found. In two cases the Kveim test gave an inconclusive reaction for sarcoidosis. Common to all cases were roentgenological findings consistent with sarcoidosis. All the patients were refractory to treatment, which ranged from the routine symptomatic care of uveitis to use of calciferol and intensive streptomycin therapy. In one case the disease resulted in total destruction of useful vision.

The protean manifestations of the disease were emphasized, and mention was made of the massive ocular tissue damage that may result. Six slides were shown.

Aneurysm of the Internal Carotid Artery Simulating Tumor: Report of A Case. Dr. Jesse M. Levitt, Brooklyn (by invitation).

This paper was published in the March 1950 issue of the Archives, page 500.

DISCUSSION

Dr. James W. Smith: Dr. Levitt has called our attention to the fact that the diagnosis and localization of an intracranial aneurysm may be simple or may be very difficult. It should be mentioned that aneurysms at the anterior end of the circle of Willis are often so small that the changes in the field of vision are inconstant and often absent.

In a case of mine, that of a woman aged 34, the diagnosis of aneurysm of the left internal carotid artery was made before rupture. The rupture occurred 11 days after the onset of blurred vision and pain in the left eye and frontal area and three days after the onset of diplopia and ptosis. A new diagnostic aid, pupillography, was utilized after operation by Dr. Otto Lowenstein. Time does not permit the presentation of his findings, which I reported in more detail in my discussion of a paper by Dr. J. R. Jaeger (Syndrome of Aneurysm of the Intracranial Carotid Artery, *J. A. M. A.* **142**:309 [Feb. 4] 1950). Two of Dr. Lowenstein's conclusions should be noted. He found abnormal pupillary reactions on the side opposite that of operation and attributed these changes to another aneurysm on the right side. Dr. Levitt mentioned a unilateral Argyll Robertson pupil described by Walsh and King (Arch. Ophth. **27**: 1 [Jan.] 1942). I have a slide illustrating this reflex. Dr. Lowenstein did not feel that the Argyll Robertson phenomenon was present in this case. He attributed the slight and inextensive movement of the pupil to synkinesis associated with the limited adduction of the left eye.

Lantern slides were shown demonstrating moderate dilation of the left pupil, the pseudo-Graefe phenomenon and the Argyll Robertson pupil. With eyes down and right the upper lid drooped normally, whereas the left upper lid retracted 2 mm. and the pupil contracted 1.5 mm.

Dr. Herman Ostrow: In contrast to the two cases which have been reported this evening is that of a man who complained of but one symptom, inability to read a micrometer, of two years' duration. He had a normal vision for distance and near vision and good range of vision. There were no changes except right homonymous hemianopsia. Nothing abnormal was found on neurologic examination. A roentgenogram of the skull showed a calcific suprasellar plaque. In view of the right homonymous hemianopsia, a flap was turned down on the left side, and a large aneurysm of the internal carotid artery was found pressing on the optic chiasm. An attempt was made to tie off the artery, but the patient showed signs of syncope and the operation was discontinued. Three months later the patient had an eruptive hemorrhage from the aneurysm and died.

Dr. Alfred Kestenbaum: Ocular disturbances associated with aneurysm of the internal carotid artery in the subarachnoid space usually appear in one of two forms. One, nasal hemianopsia, occurs when the aneurysm is just lateral to the optic chiasm. The second form consists (if the aneurysm is at the right side) of left homonymous hemianopsia combined with a central scotoma in the right eye. This picture appears if the aneurysm involves the right optic tract and the right optic nerve at the same time. Much rarer is the form, represented by Dr. Levitt's case, in which obviously the aneurysm affects the optic nerve only, but not the optic tract, and, in addition, the tissues which pass through the superior orbital fissure.

Dr. Jesse M. Levitt, Brooklyn: I should like to reemphasize that an arteriographic study should be carried out whenever aneurysm is suspected. It is considered a safe procedure and can clinch or exclude the diagnosis. Of all intracranial aneurysms those of the internal carotid artery are the most amenable to surgical treatment, as Dandy stressed in his excellent monograph (Intracranial Arterial Aneurysms. Ithaca, N. Y., Comstock Publishing Co., Inc., 1944).

Hemorrhage into the Vitreous: Aspiration of Vitreous with Reintroduction of Same Vitreous. Dr. Donald M. Shafer (by invitation).

In July 1948 a white man aged 63 was admitted to the clinic with a history of loss of sight of the left eye seven years previously from an infection after cataract operation and of use of "drops" for glaucoma in the right eye. At that time the right eye was normal except for incipient nuclear cataract, and the left eye showed an old cyclitic membrane and no light perception Three months later, after enucleation of the blind (left) eye for pain and increased tension, an extracapsular cataract extraction was performed on the right eye. This was followed by increased tension despite use of miotics, a cyclodialysis, a discission and a deWecker opening in a thick secondary cataractous membrane. Seven months after his admission the fundus reflex disappeared and a diagnosis of vitreous hemorrhage was made. The patient was transferred to another clinic service for transplantation of vitreous. At that time, March 4, 1949, vision in the remaining right eye was limited to light perception with faulty projection. Examination showed absence of the fundus reflex except for a faint glow far forward peripherally; a thick mass of proliferated lens capsule, which pushed the temporal quadrant of the iris forward, and a digital tension estimated at 45 mm. of mercury.

On April 3 a keratome section was made at the limbus temporally. A large iridectomy was followed by freeing of the mass of lens capsule with scissors. All possible vitreous (2.5 cc.) was aspirated by needle through the pupil. This vitreous was tawny yellow but relatively clear, and it was felt that the discoloration was not the cause of the lost fundus reflex. The empty eye showed no reflex ophthalmoscopically. The patient's own vitreous was returned to the eye by needle through the pupil.

On the fourth postoperative day a faint red glow was seen from the fundus. Details of the vessels and nerve head were visible on the fourteenth postoperative day, and the vision was 20/50 — 2 with correction.

The mechanism of improvement was believed to be due to the making of more blood products available for absorption after the mixing occurring in the aspiration and reinjection with the needle.

DISCUSSION

DR. WENDELL L. HUGHES, Hempstead, N. Y.: I wonder whether Dr. Shafer has considered the possibility that the blood in the vitreous was coagulated so that it could not be drawn up into the needle and that all he brought up into the needle was clear vitreous. When he reinjected the aspirated vitreous, he displaced the hemorrhagic part of the vitreous back where the shadow was seen afterward (forward and in the periphery).

DR. D. M. SHAFER: I did consider this possibility, but I cannot be sure. There did remain the black mass far forward and at 12 o'clock.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Wilfred Fry, M.D., Chairman

M. Luther Kauffman, M.D., Clerk

Regular Meeting, Jan. 19, 1950

Present Status of Retrolental Fibroplasia. DR. V. EVERETT KINSEY, Boston.

Dr. Kinsey gave a brief history of the study of this condition from the work of Terry until the present. He presented statistics of incidence in several cities and referred to the work of other authors, as well as his own. He discussed various suggested methods of treatment and their shortcomings and presented the role of vitamin E in the most recent attempt at a therapeutic solution of the problem. Dr. Kinsey expressed the opinion that a great deal more work will be required before the problem is solved.

DISCUSSION

DR. CHARLES C. CHAPPLE: I wish to make some general comments on growth, especially that of premature babies. Since most retrolental fibroplasia occurs in such infants and is a disturbance of the normal growth of the components of the eye, my remarks will apply in a general way to this disease.

The term "growth," as it will be used here, includes the growth of blood vessels and other body parts, as well as growth in stature. It is frequently considered in one or another manifestation, just as one tends to regard persons in terms of individual parts, each independent of the rest. This tendency of medicine is general and certainly is as great in pediatrics as it is in ophthalmology, but a glance shows that there is reason to regard the organism as composed of integrated and indissoluble functions and parts. For example, the hyaluronic acid present in the vitreous humor of the eye is also present in the skin and elsewhere. Presumably, any substance capable of changing it in one location should be capable of changing it wherever it may lie. The blood vessels throughout the body have much in common with those of the

eye, and each blood vessel has a nerve and each nerve a blood vessel. Both structures are nourished by the same blood, which, not being an entity, is changed in cellular constituents and composition with changes in the glands and other parts which manufacture its components and with changes in the permeability of the vessel wall.

All this is obvious and may be said as accurately of adults as of premature infants. The premature infant is unlike the adult in certain respects, however. Unlike the adult, the premature infant is about to undergo, or is undergoing, the greatest growth spurt of his life. His vessels, skin and bones, and all his other parts, are subjected to a potent growth stimulus. Normally, some of this is intrinsic, and some may be acquired from his mother. When he was born, however, he started to rely on his environment for any stimulus not inherent in his own body.

Light, particularly ultraviolet light, vitamins and certain other substances are capable of affecting growth; but they are not all equal in the capacity to affect it, and it seems that they may not all affect it in the same direction. Unfortunately, all too little is known about this property. Even vitamins are not clearly divided in this respect, although the action of some is evident. Vitamin D, for example, induces calcification, which really is the opposite of growth stimulation. Calcification is a maturation phenomenon, or, in other words, a consolidation of the gain made during the growth phase. These phases of growth and consolidation, or maturation, alternate normally on daily, monthly, seasonal and longer bases. Usually, the rhythm of the phases is regular, but stimulators of one or the other mechanism may prevail and maintain one phase at the expense of the other. Vitamin C apparently parallels vitamin D; that is, its action on the maintenance of integrity of the blood vessel wall is similar to the solidification of bone calcification, but vitamin A seems to oppose the action of vitamin C, as evidenced by the fact that an excess of vitamin A induces osseous changes which are remarkably similar to those resulting from a deficiency of vitamin C, or scurvy. But this is not unreasonable. These magic bits called "vitamins" are separated from plants and animals which made them for their own use, to activate one phase or another. On this account, they should not be expected to be synergistic in another species, when they are, in a sense, antagonistic in the species of their origin.

Since there is much evidence to support this view it is reasonable that vitamins should be investigated more fully for the direction of their effect on growth. Meanwhile, vitamins given without definite indication should be dropped from the regimen generally prescribed for premature infants until more is learned of these effects, especially on the growth of blood vessels.

I might digress here to say that the present approach to vitamin administration is to give them only to prevent deficiencies, and not because of beneficial effects known to be induced by them. The dosage standards accepted have been established largely on this basis in animals or in persons older than premature infants. These infants may require more of certain vitamins, as is often the case, or, on the other hand, and this is more important, they may require none at all of some of them. It is not inconceivable that the administration of such substances might even be harmful.

In addition to vitamins, certain vehicles previously thought to be inert have been shown to exert a strong influence on growth. One of the most striking of these is propylene glycol, with which my colleagues and I have done considerable work, and which should be regarded with suspicion until its stimulating action is established to be of the nature desired. Even liquid petrolatum U. S. P. and acetylsalicylic acid have been shown by Zondek and Aschheim to have a stimulatory effect on the calcification of bones of animals. Hence, they are growth effecters.

Because of the diversity of their chemical natures and the apparent ubiquity of growth-affecting substances, it is evident that such evaluation as was noted to be advisable for vitamins might profitably be applied to their vehicles and might be extended to include foods, in an effort to learn what might be suspected as a cause of growth disturbances of many types. It would seem especially advisable to study those to be administered to premature infants, whose immature structures can respond strikingly to a stimulus which may be incapable of damaging a more mature organism.

My remarks can be summarized as a plea for all to consider the individual as a whole and to insist on real indications before allowing indiscriminate administration of substance which may influence growth.

DR. WILLIAM O. LA MOTTE JR., Wilmington, Del.: I have heard vague reports of the possibility of vitamin E's being contraindicated in the case of premature infants; I should like to know whether Dr. Kinsey or Dr. Chapple has any comment.

DR. ELIZABETH KIRK ROSE: Is the incidence of retrolental fibroplasia really as low in Philadelphia as has been implied? In only the past six months my colleagues and I have seen three cases among 15 of our premature babies weighing under 3 pounds at birth in the premature station at the University Hospital, and Dr. Henry Lee tells me they have had three among the last 14 premature infants at Pennsylvania's Lying-In Hospital. It is distressing to watch this condition develop under one's eyes.

I should like to comment on the rate of proliferation of blood vessels in premature infants, as evidenced by the increased incidence and growth of telangiectasis or hemangiomas, and to raise the question of a relation of this phenomenon to the occurrence of retrolental fibroplasia.

DR. IRVING H. LEOPOLD: I should like to raise a question, if only to have it authoritatively denied.

Last month Dr. La Motte presented statistics from Delaware Hospital, in Wilmington, showing that the year before he started his routine observation of the fundi in premature infants the incidence of retrolental fibroplasia was very low and that during the year in which he examined these fundi regularly the incidence increased. Dr. Rose mentioned the statistics of the University Hospital, where the fundi were not examined routinely for a number of years; the incidence was then very low; now that the fundi are examined regularly, the incidence has increased. I believe the same thing is occurring in other hospitals throughout this city. Either cases were being missed in the past, or observation of the fundi at frequent intervals has something to do with the increasing incidence of the disease.

DR. HENRY F. LEE: I want to raise one other question, and I have no real data. My colleagues and I are a little concerned about the possible effects of diethylstilbestrol on the newborn infant and on the premature infant. We know, of course, that obstetricians must sometimes use the drug in very significant doses, but we are beginning to be concerned about the possible effects on the baby. I wonder whether Dr. Kinsey, in his investigation of these various series, has found any correlation between the use of diethylstilbestrol or other estrogenic substances and retrolental fibroplasia.

DR. V. EVERETT KINSEY, Boston.: I shall answer the questions in the reverse order of that in which they have been proposed. I have no knowledge about the use of diethylstilbestrol and the incidence of retrolental fibroplasia but shall inquire concerning its use.

With respect to Dr. Leopold's comment on the possibility that the process of examining babies might in itself contribute to the production of the disease, there seem to be two possibilities: first, that the risk of infection has been increased and, second, that the light of the ophthalmoscope used in making the examination may have a deleterious effect on the eyes.

With regard to the possibility that retrolental fibroplasia is the result of an infection, I suppose the most likely infectious agent would be a virus. We performed an experiment which consisted in removing the aqueous humor from the eye of a premature infant in whom the disease was in the process of developing and injected the fluid into the intravitelline vein of a chick egg. The egg was hatched and the chick was examined carefully, but no abnormality was observed. However, negative results of this kind have little or no meaning. A more extensive investigation into the possibility of virus infections, either in the infant or in the mother, would seem to be indicated.

As to the second possibility, namely, that excessive light, possibly from the ophthalmoscope, might give rise to retrolental fibroplasia, I should like to call the attention of the audience to experiments performed by Dr. A. C. Krause, who covered the eye of five premature infants for 45 days after birth and found that four of the five infants acquired the disease. More evidence against the possibility that excessive examination of the infants increases the incidence of the disease comes from the fact that in Boston for a five year period the infants were not examined routinely and the incidence, in general, was about the same is it is now, when they are being examined at intervals of about a week.

Dr. Rose has called attention to my impression that there is a low incidence of retrolental fibroplasia in Philadelphia. From information which I obtained here, and which Dr. Rose has presented, I believe my impression is not justified by the facts. It is interesting to observe, however, that where there has been a high incidence, for example, in Boston and Hartford, the disease is also present in the heavier premature infants; but that in cities where the incidence is relatively low the disease seems to be confined to infants weighing less than 3 pounds at birth. If the statistics can be trusted, this would suggest that in a place where the disease is first starting it affects the lighter premature infants first, as indeed it did in Boston; later one may expect to observe cases among the heavier premature infants.

I have also heard rumors that use of vitamin E might be contraindicated for premature infants. However, we have given literally pounds of this material, with no sign of toxic effects which could be even remotely ascribed to vitamin E.

I should like to conclude by thanking Dr. Adler for his kind remarks concerning our persistence in attempting to find the cause and means of prevention of retrolental fibroplasia.

Wilfred Fry, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Regular Meeting, March 16, 1950

Sphenoidal Fissure–Optic Canal Syndrome: Presentation of Four Cases. DR. I. S. TASSMAN.

A pathological process which involves the bones at the apex of the orbit may produce pressure on the structures which pass through the sphenoidal fissure and the optic canal as they enter the orbit. Syphilis and inflammation of the bones of the orbit, arising in the nasal sinuses especially, may produce ocular impairment, but perhaps a more important and not infrequent cause is a malignant process involving the sphenoid bones secondarily, by extension from a primary seat in the paranasal sinuses. Such a pathologic condition is of interest to the ophthalmologist, although the primary disease may be far advanced when it comes to his attention.

Ptosis and ophthalmoplegia are the most important and earliest manifestations of this syndrome and result from the pressure on the structures which enter the orbit through the sphenoidal fissure. The sphenoidal fissure transmits principally the third, fourth and sixth cranial nerves; the ophthalmic vein; the orbital branch of the middle meningeal artery (when it does not pass through the middle meningeal foramen) and the sympathetic fibers from the cavernous plexus; the sympathetic root of the ciliary ganglion, and sometimes the sensory root of the ciliary ganglion.

Various degrees of visual impairment result from pressure on the optic nerve as it enters the optic canal. The latter is closely related medially to the sphenoidal sinus and sometimes to a posterior ethmoid air cell. Often only a very thin plate of bone separates the optic canal from these structures. At times the canal makes a ridge inside the sinus. Not infrequently the sinus or a posterior ethmoid air cell may invade the small wing of the sphenoid bone, and these structures have been known to surround the canal completely.

The optic canal transmits the optic nerve, the ophthalmic artery, branches of the sympathetic carotid plexus and the orbital prolongations of the meninges, which form the sheath of the optic nerve. The complete sphenoidal fissure–optic canal syndrome therefore indicates involvement primarily of the second, third, fourth and sixth cranial nerves; the ophthalmic division of the fifth nerve; sympathetic fibers, and the ophthalmic vein and ophthalmic artery, with corresponding clinical manifestations. When the syndrome is incomplete, the optic nerve or some of the other structures are spared.

This condition has been described at various times in the past as the "sphenoidal fissure syndrome," the "syndrome of the posterior orbit" and the "orbital apex–sphenoidal fissure syndrome." In the opinion of the author, the name "sphenoidal fissure–optic canal" would designate the site of the lesion and its symptom complex more accurately.

Four cases were presented illustrating the occurrence of the sphenoidal fissure–optic canal syndrome with complete ophthalmoplegia. All had a fatal termination. In the first three cases there was extension of a carcinomatous process from the nasal sinuses. In the fourth case the primary site was in the nasopharynx. This syndrome should be suspected and the primary cause looked for as early as possible. Careful roentgenologic examination of the nasal sinuses is important as an aid in the diagnosis. In most of the cases the ocular involvement occurred when the process was far advanced and the middle fossa was already involved.

The patient is usually about 60 years of age, and recurring nosebleed with nasal symptoms is complained of early. Pain and headache are common and early symptoms. The ocular manifestations are impairment of vision, impairment of rotation and ptosis, usually on one side, which later may become bilateral. The third, fourth and sixth nerves, with portions of the fifth, are involved as they enter the orbit through the sphenoidal fissure. The optic nerve is usually involved just as it enters the optic canal.

DISCUSSION

Dr. Edmund B. Spaeth: I should like to discuss this paper, for two reasons: (1) the dismal prognosis as Dr. Tassman gave it and (2) the differential diagnosis. If the prognosis is bad in all cases, the differential diagnosis would seem to be especially important. One could fill 40 pages with differential diagnoses alone. Certainly, of paramount importance is the differentiation of this orbital apex syndrome from meningioma of the sphenoidal ridge and from the cavernous sinus syndrome. The last two conditions have much in common with the orbital apex syndrome.

Dr. Tassman's cases were all of malignant growths. The diagnosis would be difficult were it not for the finding of a primary lesion and the roentgenologic manifestations of the orbital apex extension. One may wonder whether, with an earlier diagnosis, the mortality could not be reduced if the orbit were to be cleaned out and radiation therapy used.

In one of Dr. Tassman's cases, I think it was the third, the lesion might well have been a chiasmal syndrome due to pathologic involvement of the circle of Willis. It seems that differential diagnosis in this situation is of the greatest importance. In any condition with as tragic a prognosis as this there seems to be need of every effort toward earlier diagnosis and of a different form of therapy, surgical or roentgenologic.

Retrolental Fibroplasia. Dr. Algernon B. Reese, New York.

When the incidence of retrolental fibroplasia showed such a large increase about 1943, there was uncertainty as to the correct definition of the disease. Gradually, the disease is emerging as an entity separate and apart from simulating conditions, such as persistent, hyperplastic primary vitreous and retinal dysplasia. The indications are that a

pathologic process exists in the retina of affected infants even at birth and that this serves as a predisposing factor or matrix for the progressing lesion. At about the third to the fifth week one notes the tremendous dilatation and tortuosity of the retinal vessels, hemorrhages in the retina and vitreous, gradual detachment of the retina and the development of fibrous tissue in the anterior portion of the vitreous. This active course is over at the fourth to the fifth month, and then one sees the residuum of the disease.

The indications are that vitamin E is not effective in preventing or arresting the disease. My associates and I are employing roentgen radiation in the early stages, but so far we have not had sufficient experience with this treatment to warrant any conclusions. We are also using pituitary adrenocorticotropic hormone (ACTH), as others are doing elsewhere, but it also is too early to give any assessment of this therapy. The attempt to excise surgically a sufficient amount of the pupillary tissue to permit some vision has not been encouraging. We believe that about 10 per cent of the patients have been benefited to some extent, but so slightly that we are reluctant to perform the operation.

DISCUSSION

DR. JOHN S. MCGAVIC: From all the descriptions which I have read, and from the sections which I have seen, it is my impression that the process is inflammatory. By this, I mean inflammation in its broadest sense. That is, it may be an inflammation based on bacterial or viral disease or inflammation secondary to a lack of some fundamental nutritional element. Perhaps premature infants are more susceptible to minor traumas of life. In any event, the development of the fundus picture and the reaction of the vitreous described by Drs. Owen and Owen and by others certainly indicate an inflammatory reaction. The role of the hemangiomas in the development of these various types of retrolental tissue remains to be determined.

After hearing Dr. Reese's address, one is aware of two things: 1. Histopathological studies are necessary to assure a common denominator in discussions of this disease. Such studies have been lacking in the presentations of some authors, so that one cannot be sure that one is talking about the same thing. 2. Dr. Reese has made the most valuable contribution in establishing the various types of retrolental tissue aberrations on a firm basis, as proved by combined clinical and histopathological studies.

DR. HAROLD G. SCHEIE: I had had no intention of mentioning ACTH in the therapy of retrolental fibroplasia until Dr. Reese referred to our work. Dr. George Tyner and Dr. William O. LaMotte Jr. have been routinely following the cases in our nursery, I seeing them in an advisory capacity.

We recently had a case in which retrolental fibroplasia developed while the child was taking a vitamin E preparation. In desperation, we considered giving the child roentgen therapy, but Dr. Eugene Pendergrass, professor of radiology at the University of Pennsylvania, opposed the idea. He did so because a vital area of the child's brain, as well as some of the paranasal sinuses, would very likely be affected by scattered radiation. He was particularly apprehensive, because of the sensitivity of the tissues of a premature infant. While we were dis-

cussing possible therapy with the pediatrics service, Dr. Joseph Stokes suggested treatment with ACTH. This was started shortly, and it was our impression that the condition became arrested. Before treatment the child presented the typical picture of early retrolental fibroplasia, consisting of extremely engorged retinal veins with peripheral detachment of the retina. ACTH therapy was continued about two weeks, during which time the process seemed stabilized. Treatment was then stopped, and no further change occurred for at least another four weeks. At that time a severe dermatitis developed, which prevented examination for several weeks. When the eyegrounds could again be seen, the retinal detachment had not progressed, but the central vessels had become displaced, emerging from the temporal aspect of the disk, a condition suggesting an incipient retinal fold. A short time later the child died of pneumonitis. Not only is evaluation of the effect of ACTH impossible in a single case, but it must be remembered that progress of the condition may stop spontaneously. Although the course in this case suggested arrest of the retrolental fibroplasia as a result of ACTH therapy, we do not feel prepared to make this claim with any degree of finality.

DR. IRVING H. LEOPOLD: In view of the discussion concerning the use of ACTH in treatment of retrolental fibroplasia, it should be noted that such therapy does have a theoretical reason for investigation. In 1942 Dr. Eleanor Venning, working in Dr. J. S. L. Browne's laboratory, found that in the first three to five days of a newborn infant's life the infant has an extremely low supply of the adrenal cortex hormones. Even before this it had been known that the adrenal gland is not fully developed in newborn babies but matures within a few days after birth. Could this deficiency account for retrolental fibroplasia in premature infants? If so, ACTH therapy might be helpful if it could stimulate the deficient gland to increase its secretions. Perhaps cortisone (17-hydroxy-11-dehydrocorticosterone; formerly called Kendall's compound E) or actual cortex hormones might be more effective, in view of the deficient glandular function at this time of life.

DR. ALGERNON B. REESE, New York: Dr. McGavic asked why the hemangiomas of the skin regress. I do not know, except that spontaneous regression is in general characteristic of hemangiomas of infants, even full term infants.

Dr. Scheie asked whether or not the roentgen irradiation injures the brain or the pituitary gland. By using small portals, and directing the rays only to the area that we seek to treat, we give tremendous doses in treating retinoblastoma, apparently without ill effects. I do not believe that patients with retrolental fibroplasia should get more than 2,500 r. I feel quite sure that this amount can be given without untoward sequelae.

Dr. Leopold's remarks indicate that there may be some rationale for ACTH in treatment of retrolental fibroplasia.

Book Reviews

Current Therapy 1950: Latest Approved Methods of Treatment for the Practicing Physician. By Howard F. Conn, M.D., Editor. Price, $10.00. Pp. 736. W. B. Saunders Company, W. Washington Sq., Philadelphia 5, 1950.

This is the second volume of this series of books, which are extremely valuable in that they afford a ready reference for authoritative information on the latest approved methods for treatment of disease. The list of contributors is impressive. Although the treatment of ophthalmologic diseases is not included, it is a good reference book to have in any ophthalmologic library.

Diseases of the Eye, Ear, Nose and Throat: A Textbook for Nurses. Albert P. Seltzer. Price $4. Pp. 347, with 28 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1950.

This is a textbook for nurses. This book is divided into eight parts.

Part I, which is concerned with general considerations, describes the duties of the nurse in cases of disease of the eye, ear, nose and throat. It describes briefly her relation to the patient and what is expected of her in the specialist's office and in the operating room. Part II describes the anatomy, embryology and physiology of the eye, the methods of examination and the usual diseases and their treatment which the nurse will encounter. This includes a good section entitled "Do's and Don'ts in Eye Nursing" and a section on emergencies in ophthalmic nursing. The remaining six sections concern diseases of the nose, ear and throat.

The book can be recommended highly as far as its ophthalmologic applications are concerned.

Documenta Ophthalmologica. Edited by F. P. Fischer, Utrecht; A. J. Schaeffer, Los Angeles, and Arnold Sorsby, London. Volume IV. Pp. 362. Uitgeverij Dr. W. Junk, N. Z. Voorburgwal 64, Amsterdam, Netherlands, 1950.

This volume is dedicated to Karl Wessely, who recently celebrated his seventy-fifth birthday. It also records the untimely death of F. B. Fischer, of Utrecht, one of the editorial staff, whose work, like that of Wessely, is well known in this country, both men having made many notable contributions to the physiology and physical chemistry of the eye.

The original articles are as follows:

I. The Two-Quanta Explanation

1. The Experiments of van der Velden and the Theoretical Foundation of the Two-Quanta Explanation
2. Theoretical and Experimental Observations on the Two-Quanta Explanation

II. Deviations from the Two-Quanta Explanation for Threshold-Values When the Flash-Time and the Visual-Angle of the Test Spot are Large
   1. Our Confirmation of the Two-Quanta Theory When $t < \tau$ and $d < D$
   2. Discussion of the Deviations
III. The Two-Quanta Hypothesis as a General Explanation for the Behaviour of Threshold-Values for the Several Receptors of the Human Eye
   1. The Experimental Arrangement
   2. The Peripheral Threshold-Measurements
   3. The Central-Foveal Threshold-Measurements
   4. The Mutual Dependence of the Receptors of Different Kinds in the Retina
IV. Some Properties of the Nervous System of the Visual Sense
   1. The Nerve-Elements
   2. Some Properties of the Transmission in the Nervous System
V. The Sensitivity Dependence on Wave-Length for Foveal and Peripheral Vision and the Fundamental Response Curves
   1. Introduction
   2. The Peripheral Sensitivity Measurements
   3. The Foveal Sensitivity Measurements
VI. The Quanta-Explanation and the Brightness-Impression
   1. The Experiments
   2. Discussion
      (*a*) Dependence on Time
      (*b*) Dependence on the Visual Angle
   3. Conclusion
VII. Visual Acuity
VIII. Aspects of Vision
IX. Summary

Principles of Ophthalmology. By Thomson Henderson, M.D. Pp. 230, with 630 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1950.

The title of this book is misleading. It is really a series of essays setting forth the author's own, and extremely original, ideas.

Part I describes the mammalian globe. The author makes a comparison of the various portions of the mammalian globe in a series of mammals and summarizes these general features as follows:

1. The mammalian eye is divergent, except in monkeys and man.

2. A macula subserving binocular central vision is present only in primates with parallel visual axes.

3. In quadrupeds the oblique muscles are inserted in front of the equator and act as accessory adductors.

4. In Ungulata the lateral rectus is inserted nearer the corneal margin than the medial rectus. In Carnivora and in primates the opposite holds good.

5. The mammalian globe is essentially asymmetric, with the transverse diameter of the cornea larger than the vertical.

6. Man is the only mammal in which the boundary line between the retina and the ciliary region is an ora serrata; in all other mammals it is an ora plana. The term ora retinae is one applicable to both man and beast.

7. Asymmetry of the ciliary region varies in a constant pattern in the different orders, with the nasal side invariably the smallest. Anatomic evidence implies that the temporal field is always the larger because it is opposite 1, while the field opposite 4 is the narrowest.

8. In quadrupeds the pars plana on the nasal side is abolished by the retina being projected to the base of the ciliary processes and occasionally overlapping them. This advanced position of the retina on the nasal side implements the divergent optical axis in extending the outer field of vision.

9. In bats and rodents the width of the ciliary circumference is reduced to a minimum by the ciliary processes arising from the back of the iris, as in the opossum. The widest possible field of vision is thereby obtained.

10. Man is the only mammal in which the ciliary region above is smaller than that below. This is in conformity with the physiological field of vision.

11. The ciliary muscle is unevenly distributed around the ciliary circumference, in direct ratio to the width of the ciliary region indicated above. The least muscle is thus always on the nasal side. This asymmetry implies unequal action in accommodation.

12. A circumlental space is, with few exceptions, present only in primates. The space seen in sections of the lower orders is an artefact, due to shrinking of the ciliary processes in the course of mounting.

13. The zonule in fresh specimens is a corrugated membrane. The fibers seen in microscopic sections are artefacts produced by the breaking up of the membrane in mounting.

14. In monkeys and in man the iris is composed of a loose areolar tissue with surface crypts, and therefore porous.

15. In the lower orders the iris is not porous, but a solid fibrous formation with a continuous surface layer of compact connective tissue cells. At the periphery its surface is corrugated and presents a backward kink, which projects into and obliterates the posterior aqueous chamber.

16. There is no dilator pupillae in the lower orders except, so far as the author's investigations go, in otters and seals.

17. The sphincter pupillae is well developed in the lower orders, and when it contracts the corrugations and kink in the iris are straight-

ened out, with formation of a posterior aqueous chamber. With relaxation of the sphincter the elasticity of the fibrous iris stroma comes into play, and the corrugations and kink are reformed, with effacement of the posterior aqueous chamber and dilatation of the pupil.

In part II the angle of the anterior chamber is discussed. Parts IV and V are a continuation of this subject, dealing with the intraocular pressure and glaucoma. The author's general thesis is that the intraocular pressure in the normal eye is about 10 mm. of mercury and is only recorded as normally 25 mm. of mercury because the methods of measuring the pressure lead to abnormal responses. He considers that the outflow of aqueous humor is primarily into the suprachoroidal space and that glaucoma results when this avenue of escape of aqueous humor is closed off.

Part III deals with the mechanism of accommodation. He points out that the zonular fibers are in the form of an arch and that this arch must be supported by some force. This, he believes, is due to certain portions of the ciliary muscle. He regards the ciliary muscle as having a dual nerve supply, and presbyopia as due chiefly to sclerotic changes in the muscle, rather than to hardening of the lens. His ideas of accommodation are worthy of consideration and are based on much more factual evidence than his theories of intraocular pressure.

The book as a whole is stimulating, but should be read by those who have an open mind and yet are not too easily persuaded by argument.

News and Notes

PERSONAL NEWS

Appointment of Ophthalmologist to Pennsylvania Hospital.—The appointment of Dr. John S. McGavic as ophthalmologist to the Pennsylvania Hospital, Philadelphia, was announced yesterday.

Dr. McGavic, who resigned his post as an associate professor of ophthalmology at Temple University School of Medicine to assume his duties at Pennsylvania Hospital, is also attending ophthalmologist to the Bryn Mawr Hospital, assistant pathologist at the Wills Hospital in Philadelphia and assistant professor of ophthalmology at the Graduate School of Medicine of the University of Pennsylvania.

Eye Bacteriology Laboratory.—An eye bacteriology laboratory has been established by the Banting Institute in the Department of Ophthalmology, University of Toronto. The laboratory is under the direction of Dr. H. L. Ormsby, who is assisted by Dr. G. G. Cousineau, who has been appointed a Hermant Fellow. The laboratory will serve in close liaison with the departments of ophthalmology and bacteriology. Ophthalmologists may refer their private patients to the laboratory for bacteriologic investigation.

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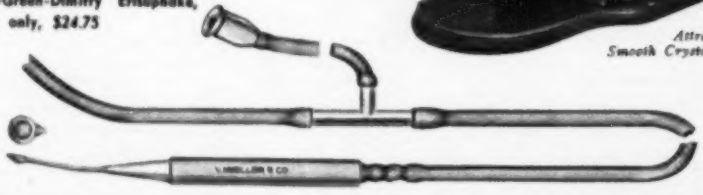

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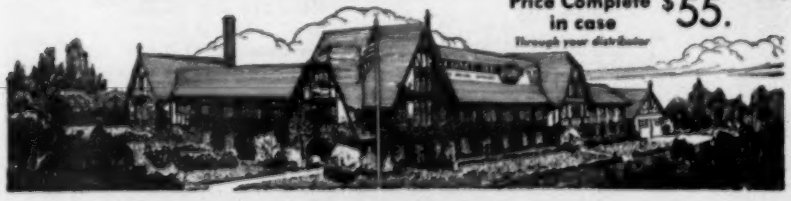

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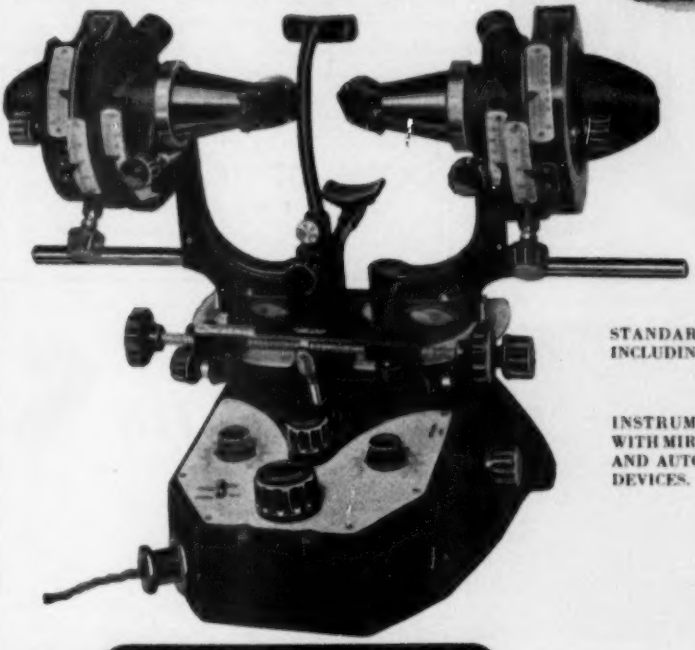

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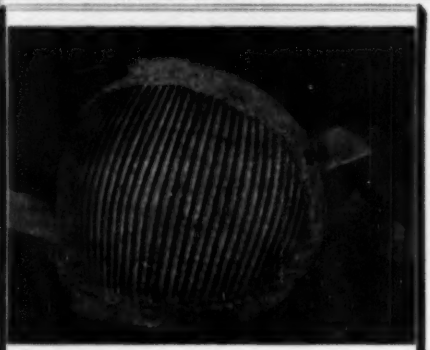

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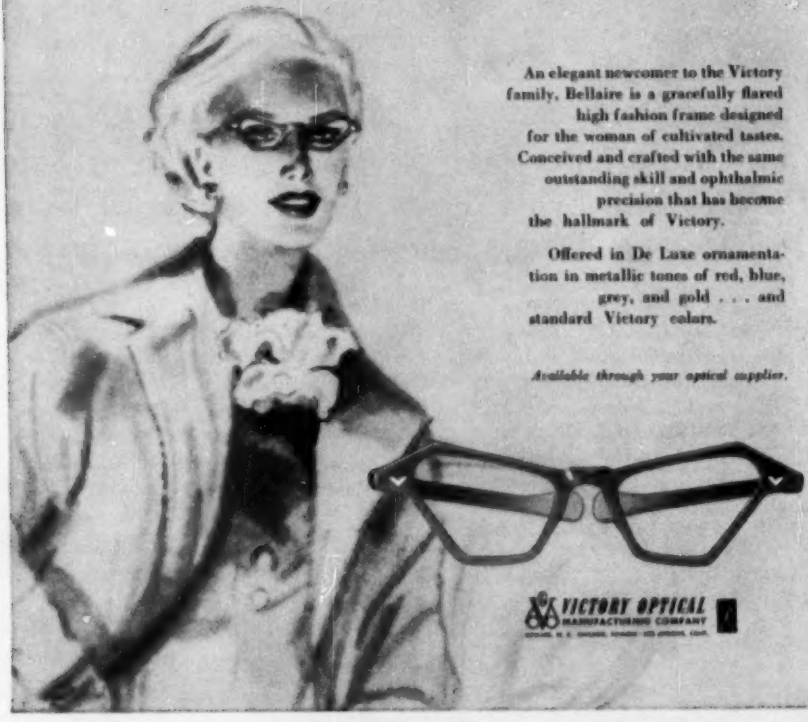

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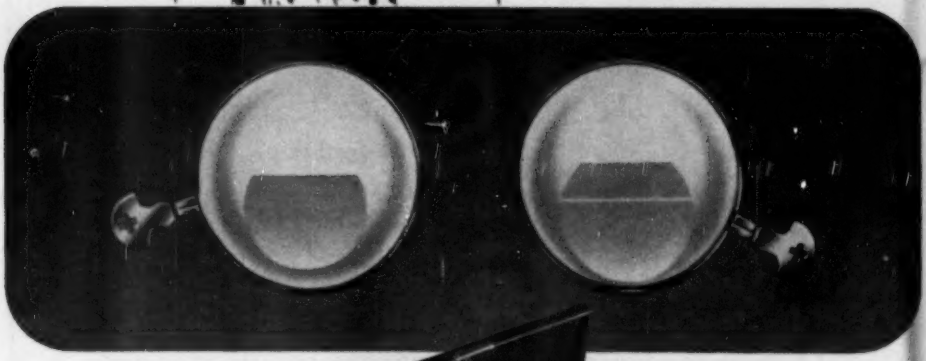

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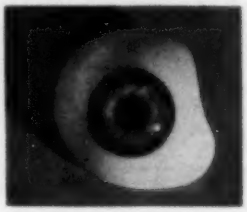

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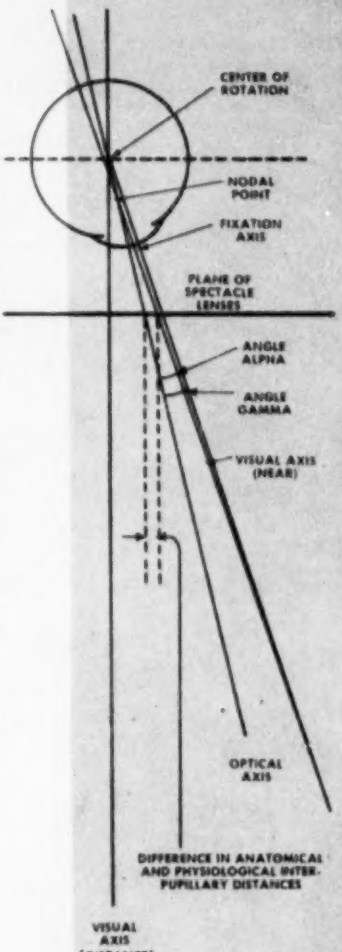

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